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A REVIEW OF FOUR DREADED COMPLICATIONS OF OPEN-HEART OPERATIONS

CAUSES, AVOIDANCE, AND TREATMENT OF ACIDOSIS, OVEROXYGENATION, HEART-BLOCK, AND PULMONARY DAMAGE

BY

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Open-heart operations using total-body perfusion may be accompanied by complications that do not commonly occur in other types of thoracic surgery. This is a review of the most important complications : metabolic acidosis (Ito *et al.*, 1957), overoxygenation (Ito *et al.*, 1958), heart-block (Olmsted *et al.*, 1958a) and pulmonary capillary damage (Kolff *et al.*, 1958). Each has been discussed in separate papers with exhaustive documentation, analysis, and bibliography.

The clinical analysis to be presented is based upon findings in 150 consecutive patients who underwent open-heart operations in the hospital of the Cleveland Clinic Foundation. The types of heart–lung machines used were the membrane oxygenator (Kolff *et al.*, 1956), the Melrose (1955) oxygenator, the Björk oxygenator (Kolff *et al.*, 1957), and the modification of the Björk oxygenator as described by Kay *et al.* (1956)[1] in combination with "sigmamotor" pumps or non-occlusive roller pumps of our own design.[2] In 75% of our patients the heart was stopped with potassium citrate according to Melrose's technique as previously described (Kolff *et al.*, 1957).

During the post-operative period radiographs of the chest were made. In each patient the first was made approximately three hours post-operatively ; the second that night ; and others during the days following if necessary.

Acidosis

Three or more hours after completion of an operation, when overventilation by the anaesthetist is no longer present, the *p*H of the blood occasionally falls to a level that is incompatible with life. Whatever the underlying cause, in these patients the mechanism of death seems to be an acidosis leading to respiratory failure followed by cardiac arrest.

Blood samples for the determination of *p*H and of CO_2 content were drawn from the inferior vena cava through an indwelling polyethylene catheter. The *p*H of this caval blood may be expected to be a little lower and its CO_2 content somewhat higher than that of the corresponding arterial blood.

The acidosis appears to be caused not by damage to the blood by the pump-oxygenator during the period of by-pass, but rather by a period of inadequate total-body perfusion as evidenced by, for example, low arterial pressure. Indeed, experimentally the *p*H and the CO_2 content of the blood can be lowered simply by reducing the cardiac output. We reduced the cardiac output in anaesthetized dogs either by partially ligating the venae cavae or by obstructing them with rubber balloons attached to cardiac catheters (Ito *et al.*, 1957). In this way the arterial pressure was reduced to 40 mm. Hg. Two hours of reduced circulation lowered the blood *p*H to about 7, notwithstanding overventilation, so that both CO_2 content and pCO_2 were low ; consequently this acidosis was not respiratory, but metabolic.

Our data on 35 consecutive patients treated with heart–lung machines conformed to the well-known fact that small children are more likely to develop acidosis than are adults. The lowest *p*H values occurred not during or immediately after, but three hours after the by-pass. Because of overventilation by the machine and by the anaesthetist, the CO_2 content for this group was lowest immediately after the by-pass and returned to a low normal value three hours later.

All patients had less than normal circulation (artificial cardiac output) during the by-pass, but, in order to detect any correlation that might exist between grossly inadequate circulation and acidosis, cases were listed according to the occurrence of "hypotension." Hypotension was regarded as being present if the mean arterial blood-pressure was less than 50 mm. Hg during extracorporeal maintenance of the circulation, or if it was less than 60 mm. Hg during the pre-run or post-run phases. The average of the *p*H values in the group with hypotension was lower than that in the group without hypotension. The data support our thesis that metabolic acidosis after open-heart operation results from the

[1] Commercially available from Pemco Inc., 5663, Brecksville Road, Cleveland 31, Ohio.

[2] Presented to us and made by Mr. Laddie C. Hercik, of the Hill Acme Company, Cleveland, Ohio.

decreased circulation. The pCO_2 was not elevated, so that the acidosis must be metabolic rather than respiratory.

Since the low *p*H and low CO_2 content follow decreased circulation, we expected the same phenomenon to occur in some patients not subjected to extracorporeal circulation, but it is rarely looked for at the proper time. Indeed, we found acidosis in other patients after periods of hypotension which followed a variety of operations. Thus to avoid the occurrence of acidosis every attempt is made to avoid periods of low perfusion as evidenced by low arterial pressure before, during, and after the by-pass. Notwithstanding these attempts, acidosis still occurs in patients when there is trouble, and especially in the very young. When a low *p*H is found or expected a standard procedure is followed: commercial sodium bicarbonate solution,[3] 4.5 mEq/kg. of body weight, is diluted with a double volume of 5% fructose in water, and started intravenously as a slow drip to be infused during the first six hours after operation. The blood *p*H is determined three and six hours post-operatively; and if the downward trend is corrected the infusion is discontinued. However, if the *p*H is still low six hours post-operatively and after completion of this dose of sodium bicarbonate, a second similar dose is started, to be administered during the next 12 hours. Sodium bicarbonate should not be given unless its need is definitely indicated, since it causes an increase of serum sodium content.

Overoxygenation

Exposure to oxygen under higher than atmospheric pressure does not occur in nature. Defence mechanisms of the organism to overoxygenation therefore cannot be reasonably expected. Our interest in preventing overoxygenation is based on our impression that it might be the cause of some sudden unexpected fatalities that occurred 10 to 12 hours after perfusion.

If a human being is exposed to a high pressure of oxygen, manifestations of oxygen intoxication rapidly appear. A common early symptom is twitching of the lips or the muscles of the arms; other symptoms are dizziness, nausea, vomiting, irregular respiration, confusion, and, in some instances, convulsions and unconsciousness (Muralt, 1954).

At atmospheric pressure, 90 to 95% of oxygen can be breathed by man for short periods without ill effects. Pichotka and Kuhn (1947) found that, in guinea-pigs and rabbits, death eventuates after continuous exposure for 75 hours.

The occurrence of retrolental fibroplasia in premature infants who have been maintained in an oxygen tent is a clear example of oxygen toxicity, notwithstanding that only the partial pressure of the oxygen was increased (Patz, 1955). In artificial oxygenators the partial pressure of oxygen can become much higher than that in the human lungs.

If pure oxygen is used in the oxygenator, overoxygenation of blood is likely to occur under the following conditions: (1) during circulation of blood through an oxygenator prior to connecting the patient to the machine; (2) during partial cardiac by-pass with a small flow rate, which is a routine procedure at the beginning and at the end of many perfusions; and (3) during perfusion of a small patient with an oxygenator of large capacity.

Though oxygenation of blood by most heart–lung machines takes place under atmospheric pressure, the partial pressure of oxygen in the oxygenators can approach 700 mm. Hg if the blood is oxygenated with oxygen plus 1.5% of CO_2 at a barometric pressure of 760 mm. Hg and at a temperature of 37° C. (the water-vapour pressure would account for 47 mm. Hg and the 1.5% of CO_2 for 11 mm. Hg). The solubility of oxygen in blood decreases with a rise in temperature (Ito *et al.*, 1958). If, for example, the temperature of the blood is 30° C. in the oxygenator and it increases to 37° C. in the patient's body, the pO_2 would increase from 700 to about 800 mm. Hg (Penido *et al.*, 1957). That overoxygenation can do no harm is unlikely, and the burden of proof seems to lie upon those who refute the evidence that it does.

To avoid overoxygenation we use the Clark polarograph[4] (Clark *et al.*, 1953). There is a linear relationship between polarographic readings and oxygen tension. On the other hand, oxygen content increases only slightly after the haemoglobin has been fully oxygenated. Thus, measurement of oxygen tension by a polarograph provides a better estimate of high oxygen values than does measurement of oxygen content or oxygen saturation.

Heart-block

Complete atrioventricular block cannot always be avoided during surgical repair of congenital malformations of the heart. It has caused many deaths, either directly after the operation or later. A-V block may be caused by surgical damage to the conductive system, but this may be reversible. It may also occur as a result of temporarily disturbed metabolism due to insufficient circulation, anoxia, potassium effect, or to other changes.

In some patients a sufficient increase in ventricular rate, notwithstanding heart-block, can be obtained with chronotropic drugs such as isoprenaline hydrochloride ("isuprel" hydrochloride; isoproterenol).[5] However, the hearts of some patients are refractory to such drugs, or become so, and a satisfactory heart rate can be obtained only by electrical stimulation.

A pacemaker provides an electrical stimulus to the ventricles when it is necessary to increase ventricular rate (Zoll *et al.*, 1956; Allen and Lillehei, 1957; Burchell, 1957; Olmsted *et al.*, 1958a). If the stimulus is strong enough, the ventricles follow the pacemaker, provided its rhythm is faster than the intrinsic ventricular rhythm. In a patient having a heart-block with a ventricular rate of 40, any ventricular rate in excess of 40 can be imposed. A pacemaker will also work in atrial fibrillation with a slow ventricular response, and, of course, also in the few patients in whom there is no atrial activity.

One elegant pacemaker amplifies the sinus waves (P waves) with transistors and a hearing-aid battery (Folkman and Watkins, 1958). This amplified impulse is applied to the ventricles. Other pacemakers generate

[3] Available in 50-ml. ampoules containing 44.6 mEq, from Abbott Laboratories, North Chicago, Ill.

[4] Commercially available from Yellow Springs Instrument Company, Yellow Springs, Ohio.

[5] Isuprel hydrochloride can be given intravenously, 0.1 to 0.5 mg., starting with 0.02 mg.; optimum dose is usually 0.04 mg. It can also be given intramuscularly or in the form of sublingual tablets (5 mg.) as often as needed.

their own rhythm. Zoll *et al.* (1956) has designed pacemakers for use with external electrodes. Kirklin (Burchell, 1957) uses that type of pacemaker with external electrodes to maintain the ventricular rate in patients having atrioventricular blocks after open-heart operations.

In many instances the heart will regain a normal sinus rhythm if the patient is maintained for a few days at an adequate ventricular rate. Even if a sinus rhythm is not restored, the heart may be given time to adjust to a low ventricular rate that is to be permanent.

When an atrioventricular block is recognized in a patient on the operating-table, even when the ventricular rate at that time is sufficient, we suture two electrodes[6] against the ventricular myocardium and lead them out of the chest through separate puncture holes. Thus the pacemaker can be used at any time when the ventricular rate becomes low. The circuit of our pacemaker has been described by Olmsted,[7] but commercially available pacemakers may be used. We believe that it is no longer justifiable to undertake open-heart surgery without a pacemaker at hand.

Pulmonary Complications

Pulmonary complications (Allen and Lillehei, 1957) were at one time a frequent cause of death in open-heart operations. However, with the recognition and elimination of many of the possible factors that lead to their development, pulmonary complications now are becoming rare.

Factors in the Occurrence of Pulmonary Complications After Open-heart Operations.—(1) Pulmonary complications occur twice as often in patients with pre-existing pulmonary vascular disease as in those without such disease. (2) It is believed that oxygen intoxication and exsiccation of the alveolar and capillary cells may follow the ventilation of the lungs by undiluted oxygen during the period of total by-pass when the lungs are not perfused with blood. We have followed the procedure of Kirklin (Patrick, 1957), who keeps the lungs gently inflated (without moving them) with a mixture of 50% helium and 50% oxygen. (3) Small children are especially likely to develop pulmonary complications because their bronchioles are small and are easily plugged with mucus or debris. Early tracheotomy may help. Postponement of open-heart operation until the child has reached the age of 2 years is recommended whenever possible. (4) Too much saline solution is present in some commercial blood-collecting bottles, and too much electrolyte or dextrose solution is sometimes given to keep the venous infusion going. (5) Air embolism originating from the right side of the heart can easily occur and does not seem to be so innocuous as was once thought. Slush (air bubbles and blood), even if it does not increase the resistance when flowing, causes a high resistance after temporary interruption of the flow (Kolff *et al.*, 1958). The forces necessary to get the slush moving again through the capillary bed may be larger than those available. (6) Temporary overloading of the pulmonary circulation with blood seems to us to be the most important single factor causing pulmonary damage. Evidence has been presented (Kolff *et al.*, 1958) which suggests that such overloading, even for short periods of time, may initiate capillary damage with various degrees of extravasation of blood. During the post-operative period these extravasations are increased by exudation and oedema until they seriously interfere with gaseous exchange.

A distressing ever-present *x*-ray finding is the increase in the pulmonary changes even when the cause of the initial damage has long since been eliminated. The pathological changes in the lungs in fatal cases usually include microscopic haemorrhages, oedema, fibrinous exudates, and, on occasion, fibrinous membranes covering or sealing the alveolar walls (Kolff *et al.*, 1958).

If the hypothesis is accepted that short periods of overloading of the pulmonary circulation can initiate capillary damage in the lungs and thereby initiate a sequence of serious events, every attempt should be made to avoid any overloading, however short its duration.

Sudden overloading of the pulmonary vascular bed with blood usually occurs by a combination of the following factors.

I. By forward overfilling:
   - A. During partial by-pass if a sudden increase in the patient's blood-volume occurs.
   - B. During total by-pass by accumulation of extravagant coronary sinus blood in the right heart.

II. Through collateral vessels:
   - A. Open ductus.
   - B. Increased bronchial circulation.

III. By retrograde overfilling:
   - A. By mechanical factors:
     1. Obstruction of pulmonary vein.
     2. Mitral stenosis.
     3. Aortic and mitral regurgitation.
   - B. Dynamic impediment (inability of the left ventricle to overcome the aortic pressure):
     1. Ventricular fibrillation.
     2. Ineffective left ventricular beat.

Forward Overfilling of the Pulmonary Vascular Bed

Overfilling by Volume Changes of the Machine During "Partial" By-pass.—Sudden decrease of the blood volume in the machine will lead to sudden increase of the patient's blood volume. This change may lead to a high venous pressure which may be passively transmitted to the pulmonary artery. Forward overfilling can be avoided by the following measures:

1. Rigid maintenance of a constant volume of the heart–lung machine will permit increase of the patient's blood volume only by intentional transfusion. The Gibbon type of oxygenator and the Clark and Gollan oxygenator (Helmsworth *et al.*, 1952) have an electrically controlled constant volume. Our Kay and Cross oxygenator (Kay *et al.*, 1956) has an electric automatic-control system (Olmsted, 1958b) that maintains the volume of the 21-in. (53-cm.) oxygenator within 150 ml. of blood.

2. Avoidance of irregularities in venous outflow. In some machines temporary difficulty with venous outflow may lead to negative pressures, which suck the walls of the venae cavae into the openings of the venous cannulae, blocking them and leading to changes in volume. This can be avoided by the use of a venous reservoir in which a slight (4 mm. Hg) negative pressure is automatically maintained (Jones *et al.*, 1955), or by the use of an open venous reservoir that can be moved up and down so that the degree of suction

[6] Twenty-six gauge stainless-steel stranded wires, 15/1,000-in. (0.038-cm.) diameter, coated with "teflon," manufactured by Falls Hollow Staybolt Co., Cuyahoga Falls, Ohio.

[7] Reprints showing circuit are available on request.

can be regulated by the height of the siphon (Lillehei, 1957). We prefer the latter (Olmsted *et al.*, 1958b).

3. Monitoring of central venous pressure through a polyethylene tube introduced via the saphenous vein into the inferior vena cava reflects the patient's blood volume immediately. This tube stays in place, and is used for determinations of venous pressures and *p*H and blood transfusion during the first post-operative days.

Accumulation of Coronary Sinus Blood Can Occur Only When the Right Atrium is Closed.—A flow of coronary sinus blood may follow a period of anoxia of the myocardium, which occurs when the occluding clamp is removed from the base of the aorta after arrest by potassium citrate. This coronary flow after anoxia may amount to 50% of the total circulation (Maraist and Glenn, 1952). Opening of the vena cava usually suffices for draining the sinus blood out towards the venous cannula of the artificial heart; occasionally a cannula in the right atrium itself is necessary.

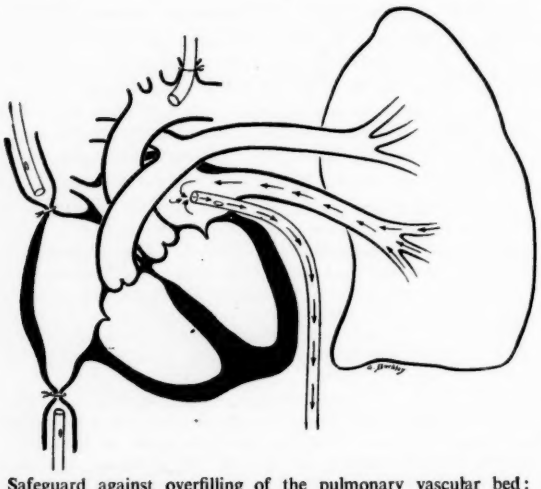
Filling of the Pulmonary Vascular Bed Through Collateral Vessels

An open ductus must be closed at the onset of extracorporeal circulation, as Dubbelman and Kolff found many years ago in very young calves (Kolff *et al.*, 1956). But if the residual pulmonary flow is small, closure before the machine is ready may cause difficulties in children. Increased bronchial circulation, as is often present in tetralogies, may lead to a large influx of blood into the lungs.

Convincing experimental proof of the importance of collateral bronchial circulation in the occurrence of pulmonary vascular overloading has been given by Muller *et al.* (1958). A cannula in the left atrium will drain off the excess blood.

Retrograde Overfilling, Mechanical (Obstruction or Insufficient Valves) or Dynamic (Insufficient Left Ventricular Contraction or Fibrillation)

Dynamic impediment to the outflow of the lungs is often overlooked. This impediment may occur when there is ventricular fibrillation or an ineffective left ventricular beat. When the patient is returned to his own circulation the right ventricle may have developed a more effective beat against the pulmonary arterial pressure than has the left ventricle against the higher pressure in the aorta; high pressures measured by us in the left atrium indicate that this may occur during the first eight minutes after arrest with potassium citrate.



Safeguard against overfilling of the pulmonary vascular bed: cannula in left atrium. This cannula is connected to a saline- or blood-filled manometer indicating the pressure in the left atrium. The cannula is also used to drain blood from the left atrium into the venous reservoir of the artificial heart. Overfilling of the pulmonary vascular bed thus becomes impossible.

A large cannula in the left atrium (see Fig.) can prevent retrograde overfilling except when there is obstruction of a pulmonary vein. A simple saline- or blood-filled manometer connected to the cannula will indicate the pressure in the left atrium. We found that the pressure in the left atrium may build up in a matter of seconds to reach 50 cm. of saline or more. If a connexion is opened to the venous reservoir which is under the level of the heart, a constant flow of bright-red blood may be observed. *Warning*: No negative pressure should be applied to the cannula if there is an open connexion of the left atrium to the atmosphere, lest air be sucked into the heart cavities.

Once the pulmonary capillaries have been damaged and the patient is in pulmonary distress, the use of a positive-pressure respirator may be life-saving.[8]

Summary

Clinical observations on 150 consecutive patients who underwent open-heart operations were corroborated by laboratory experiments. The conclusions derived were later confirmed in the open-heart operations in 330 consecutive patients.

1. *Acidosis* is most severe three or more hours after operation. It may be expected not only after open-heart operations but also after other operations, whenever a low cardiac output as evidenced by low blood-pressure has been present for a considerable time. The younger the patient the more likely it is to occur. Acidosis mainly occurs when there has been trouble, and, if severe, may lead to death unless it is controlled by intravenous infusion of sodium bicarbonate.

2. *Overoxygenation* does not occur in nature, and it is unlikely that the human organism has a defence mechanism against it, though it has not been proved to have a deleterious effect.

3. *Heart-block* can occur after operations in the neighbourhood of the A-V bundle. It is no longer justifiable to undertake an open-heart operation without a pacemaker at hand. Whenever heart-block occurs, one electrode is sewn to the myocardium before the chest is closed, even though the heart-rate while the patient is on the operating table is still satisfactory.

4. *Pulmonary complications* in open-heart operations can nearly always be avoided. The most important single measure to prevent pulmonary complications is the use of a wide cannula in the left atrium, to measure the pressure in the left atrium, and to drain out blood into the pump oxygenator if this pressure proves to be too high. Pulmonary damage during open-heart operations is usually due to temporary overfilling of the pulmonary vascular bed with blood, leading to capillary damage. The conditions under which this may occur can be predicted. Dynamic insufficiency of the left

[8] The Bennett Respirator (V. Ray Bennett and Associates, Inc., Los Angeles 48, California) provides positive pressure during inspiration only. It is best applied via a cuffed tracheotomy tube.

ventricle is perhaps the most frequent cause. Increased bronchial flow in tetralogies and open ductus are other causes.

REFERENCES

Allen, P., and Lillehei, C. W. (1957). *Minn. Med.*, **40**, 672.
Burchell, H. B. (1957). *Circulation*, **16**, 976.
Clark, L. C., jun., Wolf, R., Granger, D., and Taylor, Z. (1953). *J. appl. Physiol.*, **6**, 189.
Folkman, M. J., and Watkins, E. (1958). *Surg. Forum*, **8**, 331.
Helmsworth, J. A., Clark, L. C., jun., Kaplan, S., Sherman, R. T., and Largen, T. (1952). *J. thorac. Surg.*, **24**, 117; Discussion, p. 151.
Ito, I., Faulkner, W. R., and Kolff, W. J. (1957). *Cleveland Clin. Quart.*, **24**, 193.
—— Kolff, W. J., and Effler, D. B. (1958). Ibid., **25**, 9.
Jones, R. E., Donald, D. E., Swan, H. J. C., Harshbarger, H. G., Kirklin, J. W., and Wood, E. H. (1955). *Proc. Mayo Clin.*, **30**, 105.
Kay, E. B., Zimmerman, H. A., Berne, R. M., Hirose, Y., Jones, R. D., and Cross, F. S. (1956). *J. Amer. med. Ass.*, **162**, 639.
Kolff, W. J., Effler, D. B., Groves, L. K., Hughes, C. R., and McCormack, L. J. (1958). *Cleveland Clin. Quart.*, **25**, 65.
—— —— —— and Moraca, P. P. (1957). *J. Amer. med. Ass.*, **164**, 1653
—— —— —— Peereboom, G., and Moraca, P. P. (1956). *Cleveland Clin. Quart.*, **23**, 69.
Lillehei, C. W. (1957). "Present Indications and Contraindications for Open-heart Surgery." Presented at joint meeting of the Cleveland Surgical Society and the Academy of Medicine of Cleveland, Cleveland, Ohio, October 4, 1957.
Maraist, F. B., and Glenn, W. W. L. (1952). *Surgery*, **31**, 146.
Melrose, D. G. (1955). *J. Physiol. (Lond.)*, **127**, 51P.
Muller, W. H., jun., Littlefield, J. B., and Dammann, J. F., jun. (1958). In *Extracorporeal Circulation*, edited by J. G. Allen, p. 336. Thomas, Springfield, Ill.
Muralt, A. von (1954). In *Handbuch der Inneren Medizin*, 4th ed., edited by G. von Bergmann, W. Frey, and H. Schwiegk, vol. VI, Pt. 2, p. 310. Springer, Berlin.
Olmsted, F., Kolff, W. J., and Effler, D. B. (1958a). *Cleveland Clin. Quart.*, **25**, 84.
—— —— —— (1958b). Ibid., **25**, 169.
Patrick, R. T. (1957). *Anesthesiology*, **18**, 643.
Patz, A. (1955). Report of the 16th M and R Pediatric Research Conference. M and R Laboratories, Columbus, Ohio.
Penido, J. R. F., Swan, H. J. C., and Kirklin, J. W. (1957). *Proc. Mayo Clin.*, **32**, 389.
Pichotka, J., and Kuhn, H. A. (1947). *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.*, **204**, 336.
Zoll, P. M., Paul, M. H., Linenthal, A. J., Norman, L. R., and Gibson, W. (1956). *Circulation*, **14**, 745.

INFLUENCE OF THE PITUITARY ON THE ERYTHROPOIETIC PRINCIPLE PRODUCED IN THE KIDNEY

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This study is a continuation of a previous work (Osnes, 1959). The purpose of this report is to demonstrate the stimulating influence of the pituitary on the erythropoietic principle produced in the kidney (K.F.=kidney factor).

It is well accepted that an anaemia develops after hypophysectomy, but opinions differ regarding the mechanism of post-hypophysectomy anaemia.

Flaks *et al.* (1937, 1938) reported that the oral administration of anterior lobe of ox pituitary or extracts of anterior lobe resulted in a significantly increased erythrocyte count in both normal and hypophysectomized rats, and postulated that the anterior lobe of the pituitary contains a specific erythropoietic hormone with the bone-marrow as its target organ. Meyer *et al.* (1940) were unable to obtain the results reported by Flaks *et al.*

White and Dougherty (1945) stated that continued daily injection of pituitary adrenotrophic hormone into mice resulted in an increase in haemoglobin and in red cells. They concluded that the adrenotrophic hormone, by means of its trophic influence on the adrenal cortex, maintains a physiological control over the number of circulating erythrocytes.

A number of papers which deal with the erythropoietic effect of pituitary extracts and hormones have been published from the Institute of Experimental Biology and the Donner Laboratory, University of California (Garcia *et al.*, 1951; Contopoulos *et al.*, 1953, 1954; Van Dyke *et al.*, 1954, 1957). These investigators reported that normal rats injected with 0.5 mg. of adrenocorticotrophic hormone twice a day for 34 days showed normal haematological values, whereas after 116 days four rats showed a red-cell volume and a haematocrit level above those of normal controls. Oral administration of sheep anterior pituitary repaired the anaemia in hypophysectomized rats, and in adrenalectomized rats brought a 20% increase in circulating red-cell volume above that of either normal or adrenalectomized controls. Hypophysectomized rats injected with "pituitary erythropoietic factor" showed marked increase in red-cell volume, haemoglobin, and haematocrit. "These values were not only brought back to normal but exceeded normal value."

Based on these and other findings, the above authors postulated the existence of a pituitary erythropoietic factor distinct from the well-known pituitary hormones and with the bone-marrow as its target organ. Some of these authors felt that there also was chemical evidence for such an opinion.

Simpson *et al.* (1959), however, presented a re-evaluation of the evidence for a pituitary erythropoietic hormone and stated: ". . . there is no satisfactory evidence for a pituitary erythropoietic factor distinct from the known pituitary hormones. The adrenocorticotrophic hormone is clearly instrumental in the regulation of red-cell volume, as is thyrotrophic hormone and possibly growth and gonadotrophic hormones. The relative importance and mechanism of action of the several factors remains to be determined."

Several investigators believe that anaemia which follows hypophysectomy does not indicate any specific deficit in erythropoiesis and have claimed that the loss of the pituitary influence on the adrenals, gonads, and especially on the thyroid may be responsible for the developing anaemia. Crafts (1949) reported that in hypophysectomized rats treated with thyroxine, combined with testosterone propionate and high-protein diet, the haematocrit and haemoglobin values were maintained at normal levels and the number of erythrocytes increased above the control level.

The method used in the present work was described earlier (Osnes, 1959). To indicate the variation between the observations, ± 1 standard deviation has been calculated, and plotted in the graphs.

Experimental Findings

Fig. 1 shows the reticulocyte and haemoglobin values in a group of hypophysectomized bled rats and in a group of normal bled rats. It is seen that the reticulocytosis in the hypophysectomized bled rats was only about half the value of that observed in the normal bled controls. Many of the reticulocytes seen in the

hypophysectomized animals were small and deformed cells. After the last bleeding on the sixth day the haemoglobin value rose quickly in the normal rats, whereas the rise in haemoglobin value in the hypophysectomized rats was slight.

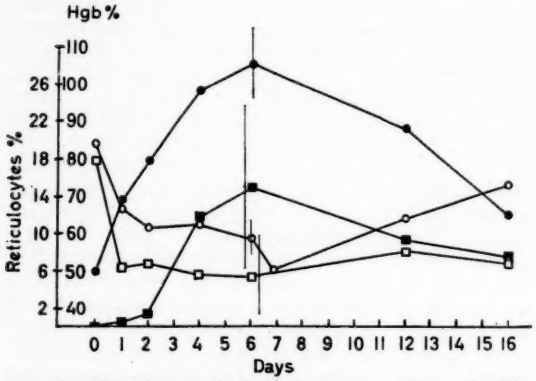

FIG. 1.—Hypophysectomized bled rats (6): □—□, Hb; ■—■, reticulocytes. Normal bled rats (6): ○—○, Hb; ●—●, reticulocytes.

The finding that hypophysectomized animals are able to react with reticulocytosis after bleeding has led some authors to conclude that there is no specific deficit in the erythrocyte production in hypophysectomized animals. This, however, may be a premature conclusion. In my experiments bled nephritic mice also have shown a reticulocytosis of nearly the same degree as bled hypophysectomized rats. The nephritic mice, however, are lacking a specific erythropoietic principle (K.F.) (Osnes, 1959).

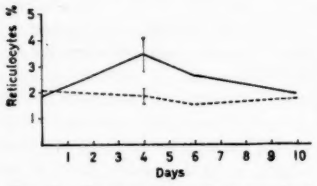

FIG. 2.—Donors: hypophysectomized bled rats (10). Recipients. ———, normal mice (10); – – – –, nephritic mice (10).

It has previously been demonstrated that serum from normal bled mice has an elevated titre of erythropoietin (produces reticulocytosis when injected into normal mice) as well as of K.F. (produces reticulocytosis when injected into nephritic mice). The titre of these two different erythropoietic principles is also found to be raised in serum from normal bled rats.

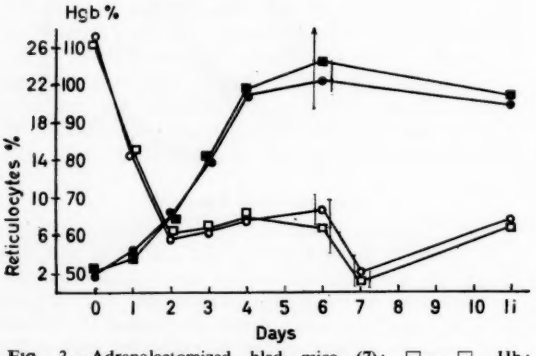

FIG. 3.—Adrenalectomized bled mice (7): □—□, Hb; ■—■, reticulocytes. Sham-operated bled mice (6): ○—○, Hb; ●—●, reticulocytes.

Fig. 2 shows an experiment where 10 hypophysectomized rats were bled to a haemoglobin value of about 30%. On the third day serum from each rat was injected into one normal and one nephritic mouse (2% of body weight). Serum from all rats gave reticulocytosis in the normal mice, but in no instance was reticulocytosis found in nephritic mice. This experiment shows that hypophysectomized rats are not able to elevate their titre of K.F. after bleeding, whereas their erythropoietin titre is elevated. These are just the same findings as demonstrated in *x*-irradiated nephritic mice and in anaemic human patients suffering from nephritis, chronic polyarthritis, and ulcerative colitis (Osnes, 1959). As K.F. is found necessary for the erythropoiesis, the present experiments indicate that the post-hypophysectomy anaemia is related to lack of K.F., and it may be assumed that some pituitary substance has a regulating influence on the secretion or production of K.F.

Fig. 3 shows the reticulocyte values and the haemoglobin values in a group of adrenalectomized mice and in a group of sham-operated mice bled to the same degree. It is seen that the reticulocyte response was the same in both groups. After the mice had been bled for six days the haemoglobin values rose quickly to the same degree in both groups. It is possible that the adrenalectomized mice possessed intact accessory adrenal tissue. The fact, however, that no difference was found in reticulocyte values between the two groups, and that the haemoglobin values rose at the same degree in both groups after bleeding, indicates that the adrenals have no fundamental influence on the erythropoiesis.

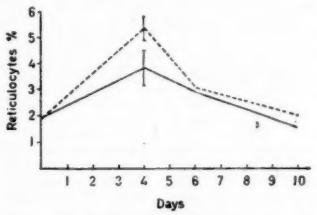

FIG. 4.—Donors: adrenalectomized bled mice. Recipients: ———, normal mice (6); – – – –, nephritic mice (6).

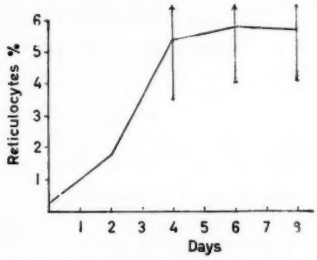

FIG. 5.—Hypophysectomized rats (6) treated with A.C.T.H.

Fig. 4 shows the reticulocytosis in normal and nephritic mice after a single injection of serum (2% of body weight) from adrenalectomized bled mice. This serum produced reticulocytosis in normal as well as in nephritic mice. In agreement with the experiments presented in Figs. 3 and 4 we must conclude that the production of erythropoietin as well as of the K.F. may go on in the absence of the adrenals. We must further conclude that the postulated pituitary substance regulating the K.F. does not act via the adrenals.

Fig. 5 shows the reticulocytosis in hypophysectomized rats injected subcutaneously with 4 mg. adrenocorticotrophic hormone twice a day. (The preparation used was "jaton prolongatum." This preparation contains carboxy-methyl cellulose saline of oxycellulose purified corticotrophin. In the following experiments the term A.C.T.H. refers to this preparation.) It is seen that hypophysectomized rats responded with considerable

reticulocytosis after injection of A.C.T.H. Because the anaemia in hypophysectomized rats is found to be related to lack of K.F. (Fig. 2) we must suppose that increased production of K.F. is the cause of the high reticulocyte response seen in these hypophysectomized rats after injection of A.C.T.H.

Increase of reticulocyte counts after injection of A.C.T.H. was found neither in nephritic nor in normal mice when the blood samples were taken at least 24 hours after the last injection. In spite of the finding that injection of A.C.T.H. may stimulate the production of K.F. in hypophysectomized rats, it is not to be expected that injection of A.C.T.H. increases the production of K.F. in nephritic mice, because the impaired production of K.F. in nephritic mice is most probably due to disease in the kidney. In normal mice, however, an elevation of the titre of K.F. without elevation of the titre of erythropoietin would not be expected to cause reticulocytosis.

With the intention of investigating whether A.C.T.H. elevates the titre of K.F. in normal mice the following experiments were done.

Normal mice were injected with A.C.T.H., and serum from these animals was injected into nephritic mice (2% of body weight). The donor group A was injected with 4 mg. of A.C.T.H. eight hours before giving serum to the recipient group A. The donor group B was injected with A.C.T.H. (2 mg. per injection) 24 and 8 hours before giving serum to the recipient group B. The donor group C was injected with A.C.T.H. (2 mg. per injection) 48, 36, 24, and 8 hours before giving serum to the recipient group C. Fig. 6 shows that reticulocytosis developed in all recipient groups. The highest reticulocyte response was seen in group B, which was injected with serum from mice treated with A.C.T.H. for 24 hours. As pointed out above, no reticulocytosis was seen in nephritic mice injected with A.C.T.H. when the blood samples were taken at least 24 hours after A.C.T.H. injection, and therefore excludes the possibility that the response seen was due to A.C.T.H. itself. The present experiments clearly demonstrate that injection of A.C.T.H. in normal mice elevates their titre of K.F., because serum from these mice causes marked reticulocyte response in nephritic mice which are lacking the K.F. This observation is of great importance for the problems discussed in this paper and is in complete agreement with the findings presented above, that hypophysectomized rats which are lacking K.F. (Fig. 2) react with considerable reticulocytosis after injection of A.C.T.H. (Fig. 5).

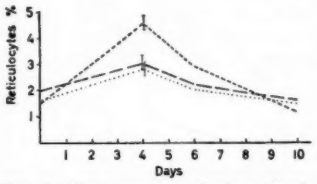

FIG. 6.—Donors: normal mice treated with A.C.T.H. at (A) 8 hours, (B) 24 hours, and (C) 48 hours. Recipients: nephritic mice treated with — — —, serum from A (4); – – –, serum from B (5); and ....., serum from C (4).

Nephrectomized unbled mice were injected with A.C.T.H. (2 mg. per injection) 24 and 8 hours before their serum was given to nephritic mice. This serum gave no reticulocyte response in the nephritic recipients. In the previous paper it was demonstrated that nephrectomized mice do not elevate their titre of K.F. after bleeding. The present experiment shows that nephrectomized unbled mice do not elevate their titre of K.F. after injection of A.C.T.H. The latter finding is fresh evidence, added to the former, that the kidney produces an erythropoietic principle (K.F.).

The findings presented above led to the conclusion that some pituitary substance has the kidney as target organ and stimulates the secretion (production) of the erythropoietic principle produced in the kidney (K.F.). One cannot with certainty exclude that the preparation used in these experiments (jaton prolongatum) may contain other active pituitary substances than the adrenocorticotrophic hormone. Therefore it is not possible from the experiments presented to tell whether the active pituitary substance is identical with the adrenocorticotrophic hormone.

If, however, the pituitary substance stimulating the secretion of K.F. is identical with the adrenocorticotrophic hormone, adrenalectomized unbled mice would be expected to have an increased titre of K.F. in their serum owing to their elevated titre of adrenocorticotrophic hormone. That this is the case is demonstrated in Fig. 7, which shows the reticulocyte response in nephritic and normal mice after injection of serum (2% of body weight) from adrenalectomized unbled mice. The adrenalectomy of the donors was performed 32 hours before giving their serum to the recipient groups. This experiment strongly indicates that the active pituitary substance is identical with the adrenocorticotrophic hormone. Serum from mice which had been adrenalectomized 52 hours previously gave only a slight reticulocyte response in nephritic mice.

It is a well-known fact that cortisone counteracts the production of adrenocorticotrophic hormone. If the pituitary substance stimulating the secretion of K.F. is identical with the adrenocorticotrophic hormone, it may be expected that large doses of cortisone will counteract the secretion of K.F. and impair the erythropoiesis. This is also the case. Fig. 8 shows the reticulocyte and haemoglobin values in a group of bled mice treated with cortisone and in a group of bled mice not treated with cortisone. Cortisone was injected subcutaneously twice a day (2 mg. of cortisone acetate in Ringer's solution to 0.2 ml. per injection) and was given two days before the first bleeding. (The preparation used was "cortone.") It is seen that the reticulocyte count in the cortisone-treated group was one quarter of the

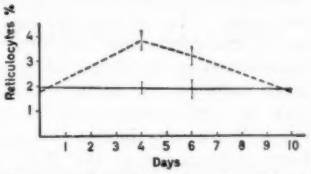

FIG. 7.—Donors: adrenalectomized unbled mice. Recipients: ———, normal mice (6); – – – –, nephritic mice (6).

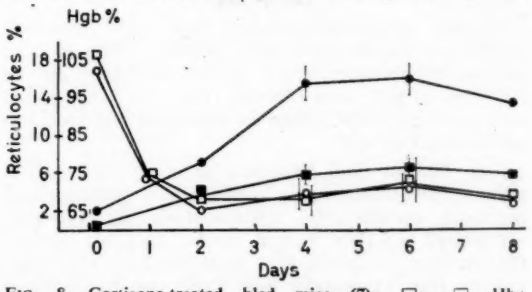

FIG. 8.—Cortisone-treated bled mice (7): □——□, Hb; ■——■, reticulocytes. Normal bled mice (6): ○——○, Hb; ●——●, reticulocytes.

normal value after injection of cortisone for two days (before the first bleeding). After bleeding, the reticulocytosis in the cortisone-treated group was less than half of that seen in the control group. Many of the reticulocytes seen in the cortisone-treated animals were small and deformed cells, similar to those seen in hypophysectomized bled rats. This experiment clearly shows that the erythropoiesis is impaired in mice injected with large doses of cortisone.

Fig. 9 shows the reticulocyte values in normal and nephritic mice after a single injection of serum from cortisone-treated bled mice. The donors were injected with 2 mg. of cortisone twice a day and were bled on the third and fourth day, and the serum was given to the recipients on the fifth day. This serum produced reticulocytosis in normal mice, but not in nephritic mice. This experiment shows that mice injected with large doses of cortisone are not able to elevate their titre of K.F. after bleeding, whereas their titre of erythropoietin is increased.

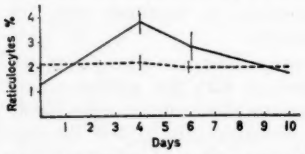

FIG. 9.—Donors: cortisone-treated bled mice. Recipients: ——, normal mice (6); – – –, nephritic mice (6).

The findings presented in Figs. 7, 8, and 9 have led to the conclusion that the pituitary substance stimulating the secretion of K.F. is identical with the adrenocorticotrophic hormone.

If the kidney is functionating as target organ for adrenocorticotrophic hormone, it may be expected that some demonstrable alteration will take place in the kidney after the influence of the adrenocorticotrophic hormone. This is also the fact. It has been pointed out in this paper that bleeding, A.C.T.H. injection, and adrenalectomy raise the titre of K.F. in mice with intact kidneys. By all these procedures, which raise the titre of adrenocorticotrophic hormone, characteristic changes are seen in the juxtaglomerular cells. It has been suggested that the K.F. is connected with the granules of the juxtaglomerular cells (Osnes, 1958, 1959). Further experiments on the relation between the titre of K.F. and the alteration of the juxtaglomerular cells have corroborated this view and are in good agreement with the assumption that the juxtaglomerular cells function as target organ for adrenocorticotrophic hormone and are the producers of the K.F. or its precursor. The findings related to the juxtaglomerular cells will be documented and discussed in a separate paper.

Discussion

Because hypophysectomized rats show impaired erythrocyte regeneration after bleeding (Fig. 1), and because hypophysectomized rats are unable to elevate their titre of K.F. after bleeding (Fig. 2), it is concluded that some pituitary substance stimulates the secretion (production) of K.F.

The findings that injection of a highly purified adrenocorticotrophic preparation (jaton prolongatum) produces considerable reticulocytosis in hypophysectomized rats (Fig. 5), and, further, that this preparation elevates the titre of K.F. in unbled mice with intact kidneys (Fig. 6), make it most likely that the pituitary substance stimulating the secretion of K.F. is identical with the adrenocorticotrophic hormone.

Because adrenalectomy alone is followed by a raised titre of K.F. (Fig. 7), because injection of cortisone depresses the reticulocytosis in normal as well as in bled mice (Fig. 8), and because cortisone-treated mice are unable to elevate their titre of K.F. after bleeding (Fig. 9), it is concluded that the pituitary substance stimulating the secretion (production) of K.F. is identical with the adrenocorticotrophic hormone.

As pointed out in this paper, adrenalectomy does not decrease the degree of reticulocytosis after bleeding (Fig. 3), and adrenalectomized bled mice as well as adrenalectomized unbled mice have an elevated titre of K.F. in their serum (Figs. 4 and 7). These findings show that the adrenocorticotrophic hormone when regulating the K.F. does not act via the adrenals.

As mentioned above, some authors have reported that they have obtained increased haemoglobin values by oral administration of anterior lobe of the pituitary or by injections of pituitary preparations. I also have found a moderate increase in the haemoglobin value in mice treated with A.C.T.H.

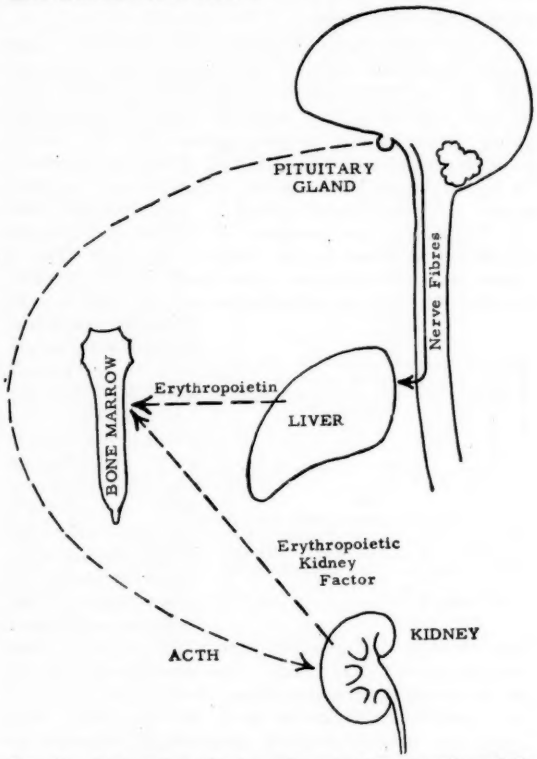

FIG. 10.—Suggested mechanism of production of erythropoietic kidney factor and erythropoietin.

In this paper it is shown that injection of A.C.T.H. into normal mice raises the titre of K.F. The increased haemoglobin values seen in A.C.T.H.-treated mice, however, do not appear to be related to an increased titre of K.F. As pointed out previously (Osnes, 1959), increased amounts of K.F. do not seem to cause increased red-cell production in normal animals. If they did it would be expected that a single injection of A.C.T.H. into normal mice would produce reticulocytosis of about 10 days' duration, due to elevated titre of K.F., and it might be expected that continued injections of A.C.T.H. would produce reticulocytosis of

longer duration. This, however, has not been found. A single injection of A.C.T.H. produced an initial rise in reticulocyte counts from about 2 to about 3% within two hours (outflow), followed by a drop to normal values after about 24 hours. A repeated injection of A.C.T.H., then, gives the same results.

By injection of 1 mg. of A.C.T.H. twice a day into normal mice it has been possible to keep the animals on a raised reticulocyte level for some time. In spite of continued injections of A.C.T.H., however, the reticulocyte counts decrease little by little, and after about 10 days the average reticulocyte counts have reached the normal level.

These findings make it doubtful whether the increased haemoglobin values seen after administration of A.C.T.H. are related to the increased titre of K.F.

The working hypothesis adopted is that the increased haemoglobin values, at least in part, may be related to an increased release of cells from the bone-marrow (outflow) caused by A.C.T.H. This release may act as a stimulus for increased production of erythrocytes. If polycythaemia tended to develop in this way, it might be counteracted by decreased amounts of erythropoiesis-stimulating substances (erythropoietin) in animals with intact mechanism for regulation of erythrocyte and haemoglobin levels. In accordance with this, no marked degree of polycythaemia seems to have been observed in animals after administration of A.C.T.H. Problems related to outflow will be discussed in more detail in another paper.

The mechanism regulating the titre of K.F. has been discussed in this paper. In a preceding paper it was shown that the titre of K.F. increases in cordotomized mice after bleeding, whereas the titre of erythropoietin does not. Two patients with hepatitis showed increased titre of K.F., whereas erythropoietin could not be detected, indicating the liver as a place of formation of erythropoietin. This suggests a mechanism in the production and regulation of K.F. and erythropoietin as shown in Fig. 10.

Summary

Hypophysectomized bled rats show impaired reticulocytosis and their titre of K.F. is not raised as in normal bled rats, whereas their titre of erythropoietin is raised.

Adrenalectomized bled mice show reticulocytosis of the same degree as normal bled mice and their titre of a specific erythropoietic principle (K.F.) as well as of erythropoietin is raised.

Hypophysectomized rats respond with considerable reticulocytosis after injection of adrenocorticotrophic preparation.

Normal mice injected with adrenocorticotrophic preparation have an elevated titre of K.F. in their serum, whereas nephrectomized mice injected with adrenocorticotrophic preparation have no traceable amounts of K.F. in their serum.

Adrenalectomized unbled mice have a raised titre of K.F. in their serum.

Mice injected with large doses of cortisone show impaired reticulocytosis and their titre of K.F. is not elevated as in normal mice after bleeding, whereas their titre of erythropoietin is.

The findings here presented have led to the conclusion that the adrenocorticotrophic hormone, by an extra-adrenal mechanism, stimulates the secretion (production) of the erythropoietic principle produced in the kidney.

I am indebted to the Norwegian Cancer Society (Landsforeningen mot Kreft) for research grants, and to Professor L. Kreyberg for providing working facilities. I thank Dr. F. Devik for stimulating discussions and for valuable assistance in the presentation of this work. I am grateful to A/S Apothekernes Laboratorium for generously placing the A.C.T.H. preparation jaton prolongatum at my disposal, and to Mr. Asbjörn Nilsen for performing the hypophysectomies in the rats used for the experiments kindly provided by Nyegaard et Co. A/S.

REFERENCES

Contopoulos, A. N., Ellis, S., Simpson, M. E., Lawrence, J. H., and Evans, H. M. (1954). *Endocrinology*, **55**, 808.

—— Van Dyke, D. C., Simpson, M. E., Garcia, J. F., Huff, R. L., Williams, B. S., and Evans, H. M. (1953). *Blood*, **8**, 131.

Crafts, R. C (1949). *Endocrinology*, **45**, 159.

Flaks, J., Himmel, I., and Zlotnik, A. (1937). *Presse méd.*, **45**, 1261.

—— —— —— (1938). Ibid., **46**, 1506.

Garcia, J. F., Van Dyke, D. C., Huff, R. L., Elmlinger, P. J., and Oda, J. M. (1951). *Proc. Soc. exp. Biol. (N.Y.)*, **76**, 707.

Meyer, O. O., Thewlis, E. W., and Rusch, H. P. (1940). *Endocrinology*, **27**, 932.

Osnes, S. (1958). *Brit. med. J.*, **2**, 1387.

—— (1959). Ibid., *2*, 650.

Simpson, M. E., Evans, E. S., and Rosenberg, L. L. (1959). *Endocrinology*, **64**, 592.

Van Dyke, D. C., Contopoulos, A. N., Williams, B. S., Simpson, M. E., Lawrence, J. H., and Evans, H. M. (1954). *Acta haemat. (Basel)*, **11**, 203.

—— Simpson, M. E., Contopoulos, A. N., and Evans, H. M. (1957). *Blood*, **12**, 539.

White, A., and Dougherty, T. F. (1945). *Endocrinology*, **36**, 16.

RESPONSE OF CUBAN CHILDREN TO ORAL VACCINATION WITH LIVING ATTENUATED POLIOVIRUS VACCINES

A CLINICAL AND SEROLOGICAL STUDY

BY

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Paralytic poliomyelitis occurs in Cuba as a sporadic disease in early childhood, with periodic relatively small outbreaks. Most of the cases are in children under 5 years of age, and less than 15% are in those over 10 years. In the period 1946 to 1957, with the exception of three years, the annual number of reported cases varied from 10 to 100. In 1946, 1952, and 1955 there were reported respectively 343, 494, and 267 cases (Pan-American Sanitary Bureau, 1958a, 1958b). Paul, Melnick, and Riordan (1952) suggest that perhaps only 50 to 75% of the actual cases occurring in Cuba are recorded. These authors collected 82 sera in a 1950 survey, and demonstrated the presence of Lansing-type poliovirus antibodies in 64% of the children aged 1 to 4 years and in 75% of those aged 5 to 9 years.

Our data indicate that all three types of poliovirus are widespread in the Havana metropolitan districts, and

additional studies now in progress will greatly expand the surveyed areas and the age-group samples. While Salk-type vaccine was administered to several thousand individuals shortly after this product became available, it has had no national sponsorship, and its use has been largely restricted to the practice of a small number of paediatricians and in a few institutions.

The use of the Salk-type vaccine presents a number of problems for countries whose social and economic conditions are like those of Cuba. For this reason, and because of the long and successful use of smallpox and yellow-fever live virus vaccines in Latin America, the initiation and pursuit of the work with oral attenuated poliovirus vaccines by the Lederle group (Koprowski, Jervis, and Norton, 1952), and the later entrance of Sabin (1955) in this field have been followed with great interest.

After contact with Dr. H. R. Cox, of Lederle Laboratories, and consultation with Dr. F. L. Soper, then Director of the Pan-American Sanitary Bureau, a series of studies were undertaken in Cuba. It has been possible to explore several aspects of oral poliovirus vaccination in different groups of subjects under close medical supervision. Their ages ranged from 1 to 21 years, but most were between 5 and 12. Less than 10% of those vaccinated belong to "open" groups. These were dispensary patients on whom follow-up work was difficult or impossible in a few instances. Most of the children were members of what might be called institutional populations. These included several successive groups of underprivileged children who resided in recreation camps for 90-day periods, occupants of a foundling home and an orphanage, as well as children who lived in a Cuban "boys town"* and others who attended dormitory schools but often returned home for week-ends. Observations are being continued on several of these, but serological data are now complete on the six groups which are the subject of this report.

The vaccines for these studies were provided by the Lederle Laboratories Division of the American Cyanamid Company, and the serological assays were done in its Viral and Rickettsial Research Laboratory by methods described elsewhere (Cox *et al.*, 1960) and at the Microbiological Associates Inc. laboratory in Washington, D.C.

Group 1

Since the swallowing of capsules is usually difficult without the aid of fluids, this test was designed to determine whether or not the highly acid carbonated beverages commonly enjoyed by children would inactivate the strains of vaccine virus if ingested with the virus-containing capsules.

For this trial 16 children (10 males and 6 females) aged 4 to 11 years were selected. They were daily dispensary patients at Mantilla, a suburb of Havana. Twelve of them were white. They were residents of multiple-family dwellings in an economically depressed area. Many were harbouring a variety of intestinal parasites and most of them were undernourished.

The capsules containing the vaccine strains of poliovirus were administered at intervals of 21 days in the following order and contained the indicated concentrations of virus per capsule: first feeding, type II, $10^{4.9}TCD_{50}$; second feeding, type I, $10^{4.8}TCD_{50}$; third feeding, type III, $10^{5.2}TCD_{50}$. Each child was given approximately 100 ml. of a popular beverage, having a *p*H of 3.2, with which to wash down the capsules. The children were not all started on the programme at the same time, but the first feeding was done on February 19, 1958, and the entire group had received all three strains of virus by April 18. A blood sample was collected from each child at the time of the initial feeding and again 26 to 28 days after administration of the third feeding. The sera were refrigerated until both the pre- and post-vaccination samples from all children had been obtained. The paired sera from each child were titrated simultaneously.

The serological titrations showed that at the time of the first feeding 8 of the 16 children lacked antibody for one or more types of poliovirus. The distribution of these sero-negatives was as follows:

Type I only	2	Total negatives:	
,, III ,, ...	3	Type I ..	4
Types I and III ..	1	,, II ..	2
,, II and III ..	1	,, III ..	6
,, I, II, and III ..	1		

The post-vaccination sera contained only two negatives, both for type III virus; thus the conversion rate was 83%. In addition fourfold or greater booster responses were observed in many of the children who possessed antibody prior to feeding.

The general level of response for each of the three types of poliovirus is indicated by the pre- and post-vaccination geometric mean titres and fold gains (Table I). The two type III negatives that failed to respond occurred in a 6-year-old who was previously negative only for this strain and a 7-year-old who was negative for both types I and III. These were the only type III misses in the 6- and 7-year-old children of the entire study, which included the total of 22 type III negatives (see Chart). The 7-year-old had excellent responses with both types I and II, these being from 1:4 to 1:128 and from 1:256 to 1:1,024 respectively. Since the other four type III negatives all responded satisfactorily it cannot be concluded that this virus strain is more readily inactivated than the other strains by an acid beverage such as that employed.

TABLE I.—*Group* 1. *Geometric Mean Antibody Titres*

Poliovirus Type	Before	After	Fold Gain
I	33	111	3·4×
II	128	412	3·2×
III	15	38	2·5×

The clinical observations on this and the succeeding five groups are discussed collectively below.

Group 2

At the suggestion of Dr. H. R. Cox it was decided to reinvestigate the problem of feeding all three virus strains simultaneously. For this purpose 62 female children, aged 4 to 17 years (median 10 years) were chosen: 55 were white. They were residents of what may be described as a dormitory school in the environs of Havana. The girls lived in the institution, but were free to return to their homes for week-end holidays every three to four weeks. The school was operated by the Church, and many of the children held scholarships contributed by various charitable organizations. The students represented families of modest incomes, and they were healthy and well nourished.

*A "city" for orphan and destitute children similar to Father Flannagan's in "Boys-Town," Indiana, U.S.A.

All the children were fed on May 13, 1958, at which time a blood sample was collected from each. Post-vaccination sera were obtained 38 days later. The same three lots of vaccine employed in group 1 were used in this trial. Each child received one capsule of type I, one of type III, and two type II poliovirus simultaneously, 30 minutes after a meal. The swallowing of the capsules was facilitated by the ingestion of approximately 100 ml. of a suspension of non-fat dry milk solids (" star-lac "). The girls were under the daily observation of nuns, and were visited at frequent intervals by the staff physician.

Serum neutralization tests on the pre-vaccination sera revealed 36 sero-negatives among the 62 children. They were distributed in the following combinations:

Type I only	1	Total negatives:	
,, III ,, ...	12	Type I ..	11
Types I and II ..	2	,, II ..	4
,, I and III ..	7	,, III ..	21
,, II and III ..	1		
,, I, II, and III ..	1		

The post-vaccination serum studies disclosed four residual negatives. An 11-year-old, negative only to type I prior to vaccination, and a 12-year-old who had been negative for both types I and II, had both failed to respond to type I strain. The other two misses were for type III virus, one in an 11-year-old, negative only for type III, and the other in a 14-year-old who had been without antibodies for type II and III before the simultaneous feeding of all three virus strains. The conversion rate for the pre-feeding negatives was 89%, and, in addition, 21 out of 50 children whose antibody titres had ranged from 1:4 to 1:512 in their pre-vaccination sera manifested fourfold or greater gains in titre. The composite antibody gains are reflected in the geometric mean titres before and after simultaneous virus feeding (Table II).

TABLE II.—*Group* 2. *Geometric Mean Antibody Titres*

Poliovirus Type	Before	After	Fold Gain
I	35	126	3·6×
II	162	462	2·8×
III	13	115	8·8×

It is of interest to note that the triple negative in this group, a 10-year-old girl, responded with titres of 128, 16, and 1,024 for types I, II, and III respectively.

Group 3

In order to gain some information regarding the flexibility of the feeding schedule, 91 children (50 males and 41 females) were fed the three strains of poliovirus with a 7-day interval between the ingestion of each type. Their ages ranged from 6 to 11 (median 8 years), 72 of the children being white. All were residents of the Matanzas City Recreation Camp. They were heavily parasitized and came from the poorest economic strata of the rural areas, where malnutrition is a way of life. The children stayed for 90 days in the recreational camp, and during this time were well fed and well cared for. The primary activity of the resident physician at the camp is to restore the health of the children, rid them of parasites, and return them to their homes in good physical condition. The camp is approximately 75 miles (120 km.) east of Havana. The first feeding was two capsules of type II virus containing $10^{5.3}TCD_{50}$ of virus on September 6, 1958. A week later the children were fed two capsules of type III virus containing $10^{5.6}TCD_{50}$, and the final feeding was $10^{5.5}TCD_{50}$ of type I virus in a single capsule. At each feeding the children were given a glass of fat-free dry milk with a *p*H of 6.7. Serum samples were collected at the time of the first feeding and 34 days after the administration of the type I strain.

At the time of the primary feeding there were 23 sero-negatives, distributed among 16 children as follows:

Type I only	5	Total negatives:	
,, II ,, ...	1	Type I ..	10
,, III ,, ...	3	,, II ..	3
Types I and III ..	5	,, III ..	10
,, II and III ..	2		

Post-vaccination serum-neutralization tests showed that the negative-to-positive conversion rate was 96%. A single type I negative remained. This was in a 9-year-old girl who had previously been without antibodies for both types I and III poliovirus; her type II titre remained unchanged at 1:512.

In addition to the 22 negatives which were converted, 21 out of 71 children whose pre-vaccination titres ranged from 1:4 to 1:512 showed booster responses for type I virus, 20 out of 55 for type II, and 59 out of 76 for type III. The magnitude of the collective response is suggested by the geometric mean antibody titres before and after feeding the three virus types at seven-day intervals (Table III).

TABLE III.—*Group* 3. *Geometric Mean Antibody Titres*

Poliovirus Type	Before	After	Fold Gain
I	72	159	2·2×
II	371	709	1·9×
III	56	382	6·8×

Group 4

In a foundling home near the centre of Havana, where the majority of children had received two or three doses of Salk vaccine, an opportunity was afforded to observe the response of children to oral vaccination after artificial immunization. It is not to be presumed that their pre-vaccination antibodies were entirely the result of the Salk vaccine. The group of 105 children included 20 who had had no Salk vaccine; 10 who had received two vaccine injections, the second being given in April, 1957; and 75 who had completed their third Salk injection in May, 1957, approximately 18 months prior to the initiation of the oral vaccination programme on November 27, 1958.

Approximately 80% of the children had been resident in the institution for several years. Their ages varied from 4 to 10 years, the median being 7 years. One child was an epileptic. Fifty-six were white; 95 were males. A physician was in residence at the home. Eighteen children who had received three Salk vaccine injections and who were randomly located in dormitory quarters, were left as unvaccinated contact controls at the time the other children were given the oral poliovirus vaccine.

Capsules containing $10^{5.0}TCD_{50}$ of type II virus were administered on November 27, 1958; and on December 17, $10^{5.5}TCD_{50}$ of type III virus was fed. The final capsule, representing $10^{5.5}TCD_{50}$ of type I poliovirus, was ingested on January 20, 1959. Approximately 100 ml. of the resuspended dry fat-free mild solids at *p*H 6.7 was given with each feeding. Blood samples were collected from the vaccinated and control children at the time of the first feeding and again 34 days after the last strain was fed.

At the time the feeding programme started there were 15 sero-negative children given oral vaccine. They were distributed as follows:

Type I only	..	..	1
,, II ,,	..	..	4
,, III ,,	..	..	4
Types I and II		..	1
,, I and III		..	1
,, II and III		..	1

Total negatives:		
Type I	..	3
,, II	..	6
,, III	..	6

In addition, there was a single negative (type III) among the control children who had received three Salk vaccine injections.

Examination of the post-vaccination serum specimens revealed five residual negatives in the orally vaccinated children, a conversion rate of 67%. The type III negative control child was still negative and still unchanged in titre for the other two strains. Four of the five post-vaccination negatives were for type II virus, and three of these were in children who had had no Salk injections. While only 10 of 15 negatives converted, there were many booster responses among those whose pre-feeding antibody levels were from 1:4 and 1:512. Only one of the control children who had been in contact with the orally vaccinated children, but had not received the live virus vaccine, manifested a fourfold increase in titre for type II virus. Distributed among the other 17 unvaccinated controls there were nine instances of a twofold titre increase, 13 of a twofold titre decrease, and four in which there were fourfold titre decreases.

The composite titre changes for subgroups are illustrated by the geometric titres before and after the feeding programme was started (Table IV).

TABLE IV.—*Group 4. Geometric Mean Antibody Titres*

History of Salk Injections	No. of Children	Type I			Type II			Type III		
		Pre	Post	Fold Gain	Pre	Post	Fold Gain	Pre	Post	Fold Gain
None ..	20	54	194	3·6×	79	187	2·4×	24	132	5·5×
Two ..	10	157	294	1·9×	415	446	1·1×	79	208	2·1×
Three ..	57	229	386	1·5×	496	711	1·4×	109	288	2·6×
Controls	18	246	237		438	406		114	87	

Group 5

This trial, like that with group 3, was carried out in a recreation camp about 50 miles east of Havana. The group consisted of 111 children, of whom 77 were white; 59 were male. They ranged in age from 6 to 12 years, with a median of 8 years. The conditions of the camp and in the homes from which the children came were comparable to those described for group 3.

Beginning on September 13, the children were fed two capsules of type II virus containing $10^{5.0}TCD_{50}$ of virus; seven days later two capsules, each representing $10^{5.2}TCD_{50}$ of type III virus; and a week later a single capsule of type I virus containing $10^{5.5}TCD_{50}$. A blood sample was collected from each child at the time of the first feeding and again four weeks after the feeding of the type I virus.

During the period of virus feeding 15 of the children developed clinical influenza. Six of the affected children were 6 years old and the others were scattered in age distribution.

Serum neutralization tests showed that at the time of the first virus feeding there were 38 sero-negatives among 33 of the children. These were distributed as follows:

Type I	..	..	8
,, II	..	..	4
,, III	..	..	16
Types I and III		..	5

Total negatives:		
Type I	..	13
,, II	..	4
,, III	..	21

Post-vaccination sera were found to include one type I and one type III negative; thus the conversion rate was 94.7%. Neither of the residual negatives was in a child who suffered from influenza during immunization.

In addition to positive results in those who were previously without antibody, there were fourfold or greater increases in titre among those whose pre-vaccination levels varied from 1:4 to 1:512. The booster response rates for such children were 41% for type I virus, 66% for type II, and 75% for type III.

The general response to vaccination is shown by the increases in geometric mean antibody titres (Table V).

TABLE V.—*Group 5. Geometric Mean Antibody Titres*

	Type I			Type II			Type III		
	Pre	Post	Fold Gain	Pre	Post	Fold Gain	Pre	Post	Fold Gain
All children ..	43	123	2·9×	130	417	3·2×	19	190	10×
Children having influenza ..	58	134	2·3×	140	445	3·2×	12	140	12×

Group 6

In November, 1958, 159 inmates of a girls' institution were vaccinated with the three strains of oral poliovirus vaccine. The same lots of vaccines as those used in group 5 were employed. The feeding order was types II, III, I, with a seven-day interval between feedings. The capsules were administered with approximately 100 ml. of resuspended dry milk solids at *p*H 6.7, 30 minutes after a meal. Two doses of Salk vaccine had been given to 121 of the children in November, 1957, one year prior to the initiation of the oral vaccination programme.

The ages of the girls ranged from 6 to 19 years. The median age of the 38 who had received no Salk vaccine was 9 years, while that of those who had been given two injections of Salk vaccine was 12. Pre-vaccination serum samples were collected from each child at the time of the first feeding, and a second sample was obtained approximately one month after the third feeding.

Serological study of the blood specimens revealed a total of 15 sero-negatives at the beginning of the feeding programme (Table VI). After oral vaccination the

TABLE VI

Poliovirus Type	No Salk	2× Salk	Total Negatives
I	1	2	4
II	1	0	4
III	2	3	7
I and II	1	0	
II and III	2	0	
Totals ..	7	5	15

serum studies showed that one child remained without demonstrable antibody for type I virus and two without antibody for type II. The conversion rate was therefore 80%. The residual negatives were, for type II virus, 7- and 8-year-old children who had not received Salk vaccine, and the type I negative was a 14-year-old girl who had been Salk-vaccinated.

Table VII shows the booster response rates among children with antibody titres varying from 1:4 to 1:512 prior to vaccination with the oral poliovirus vaccine. The general responses of the two subgroups are reflected in the geometric mean titres of their poliovirus antibodies pre- and post-vaccination with oral poliomyelitis vaccine.

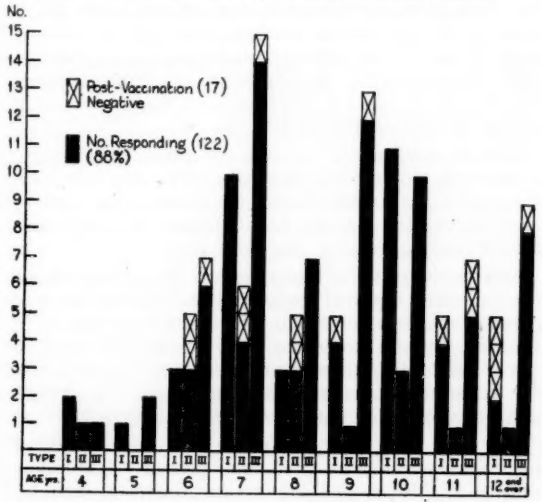
TABLE VII

	Type I	Type II	Type III
No Salk vaccine	36%	33%	53%
2 Salk injections ..	22%	28%	35%

TABLE VIII.—*Group 6. Geometric Mean Antibody Titres*

	Type I			Type II			Type III		
	Pre	Post	Fold Gain	Pre	Post	Fold Gain	Pre	Post	Fold Gain
No Salk vaccine	102	125	1·2×	73	140	2·0×	34	110	3·2×
2 Salk injections	135	139	1·0×	272	253	0·9×	110	167	1·4×

In the six groups there were a total of 139 sero-negatives. Of these, 17 were still negative after vaccination. This represents a conversion rate of 88%. The distribution of the 139 sero-negatives according to age of individual and virus type is shown in the Chart.



Combined data on distribution of poliomyelitis sero-negatives among 526 children, by age and virus type, before and after oral vaccination with poliovirus vaccine.

Discussion

In addition to these six groups vaccinated with the oral poliovirus vaccine described above, we have vaccinated eight other groups during the past year. The 14 groups comprised approximately 2,000 subjects. In none of these have nervous symptoms or other disturbances been observed which were suspected of association with the administration of the vaccines. Not only was the clinical course of the normal children entirely uneventful while undergoing immunization, but so also was that of many children who developed acute infectious diseases, such as mumps, rubella, or influenza, while participating in the oral vaccination trials. Similarly, there were no adverse reactions in one epileptic, one diabetic, and several children suffering from cardiac and kidney ailments. There were numerous minor illnesses, such as are invariably seen in undernourished, parasitized children when brought together in recreation camps and institutions, but these illnesses were no more numerous and no more severe than those observed prior to the initiation of the oral poliovirus vaccination.

We believe it is important to record that the infectious diseases mentioned above were not aggravated in any way by their concurrence with an induced infection with attenuated strains of poliovirus. Conversely, it is equally important to find that these induced infections are not altered in any clinically discernible manner by the presence of certain common diseases of childhood which are likely to occur during an immunization programme.

Since the serological studies on a large proportion of these 2,000 subjects are not yet completed it remains to be determined whether or not concurrence of these fortuitous acute infections has adversely affected the establishment of the vaccine strain in the gastro-intestinal tract. A number of vaccinated children were undergoing mepacrine treatment for infestations with *Giardia lamblia*, and this may have adversely affected the outcome of the oral vaccination. Completion of the serological tests on the sera of these individuals should provide answers to these important questions.

It should be emphasized also that several of these small-scale trials were conducted under conditions that were not likely to be favourable to the vaccines. This was done because it was thought desirable, as a guide in planning future and larger-scale programmes, to know or to have some indication of what might be expected when administrators encounter the numerous conditions and complications that are certain to develop with expanding use of the vaccine under all conditions. Our experiences to date have been most reassuring, and therefore we plan to continue our studies and to seek evidence of circumstances and conditions, both medical and environmental, which may contraindicate the use of the vaccines.

Though small in scope and number of subjects, the first trial provided an indication that common carbonated beverages having a high degree of acidity were not markedly inhibitory when consumed immediately after the ingestion of the vaccine strains in capsule form. Group 2 was large enough to give clear evidence of the fact that the simultaneous administration of all three strains can be a practical, effective procedure. This fact, now confirmed by other larger trials, is of great practical importance. The result in group 3, contrary to expectation, implies that interference between these three strains of poliovirus is not a major factor when they are given at intervals of seven days in the order: types II, III, I, since 22 of the 23 negatives converted and many of the 91 children showed good booster responses to this system of administration.

While the fourth trial provided no substantial evidence of contact spread of the vaccine strain under our test conditions, the relative titre stability of the controls during the trial period of approximately 12 weeks underscores the significance of titre changes yielded by the assay method. The number and magnitude of the responses in the vaccinated children were not remarkable, in part perhaps because of the relatively high pre-vaccination titres.

Group 5 gave similar information to that of group 3. The concurrent influenza observed in a number of children in this group was not affected by immunization with poliovirus, nor was the induced infection with poliovirus altered by the presence of the influenza. Neither of the children who failed to respond to immunization in the group was among those experiencing influenza. The children with influenza responded in the same manner to immunization, qualitatively and quantitatively, as those without concurrent influenza.

The sixth trial resembles somewhat the fourth in the general population involved, the ages represented, and the history of Salk injections. The most interesting point of comparison is the fate of sero-negatives (there were 15 sero-negatives in each group, 10 of which occurred in non-Salk-injected individuals) in the light of the different schedules of administration employed. In the fourth group, in which the capsules were fed individually over long intervals (three to five weeks) the conversion rate was 70%. In group 6, seven-day intervals were used and the conversion rate was 80%, suggesting that interference among the three strains of virus fed is not a problem.

In the six trial groups described above there were 526 children who were fed all three types of virus and from whom pre- and post-vaccination samples of sera were assayed for antibodies. Most of the children were between 6 and 10 years of age, and they represented a variety of social and economic conditions which are typical of those to be encountered in Cuba and many other Latin American countries. The results obtained in terms of responses to the three strains of poliovirus have been somewhat variable, but so have the test conditions. Some of the groups have been too small to give clear-cut answers, but they have been useful in spite of this limitation. An inherent invariable in all such studies is the degree of pre-existing immunity for each type of virus as indicated by antibody levels. Our subjects were selected on the basis of availability rather than whether or not they represented optimum media for obtaining results that would be most favourable to the vaccines. For this reason we believe that we are observing the performance of the oral vaccines in a reasonable cross-section of conditions as they exist in the field.

In assessing the value of the vaccine there are several criteria that may be applied. First, of course, is that of safety, and this we have already discussed. Second is the reduction of the hazard of paralytic poliomyelitis by the elimination of susceptibles. The conversion rate was approximately 88% in the six trial groups. The few failures have been scattered over the whole age range investigated, and they have not been confined to a single type of virus, as can be seen in the Chart.

In individual trials the conversion rates ranged from 67 to 96%. When the three strains of virus were fed simultaneously the rate was 89%. Associated with the reduction of the number of susceptibles is the frequency of booster responses. Directing attention to those children whose pre-vaccination titres varied from 1:4 to 1:512, because the titrations were not done at dilutions high enough to detect fourfold increases at levels higher than 152, 36% of 329 children had booster responses for type I virus, 45% of 287 for type II, and 62% of 328 for type III. The mean titres show clearly that the least gains were made in groups which had the highest antibody levels at the time of feeding. Gains for type II virus in general were less marked than for the other two types of virus. Fortunately, this is the type which appears to be associated with epidemics least often, and further work in the selection of strains will doubtlessly provide a blend of more equally balanced strains for the oral vaccine. We believe that the collective data argue effectively for the efficiency of the present strains and the method of application.

Another criterion that may be applied in evaluating results of our trials is that of practicality and utility of the method of application. Here there would appear to be a strong argument in its favour. With the increasing evidence of the high response rates to the simultaneous feeding of all three strains of virus, vaccination against poliomyelitis is transformed from a clinical procedure into a beautifully simple tool for mass application. It lends itself to emergency conditions as well as to the less urgent demands of routine prophylaxis in the clinic, the office, or institution. As regards speed and ease of application, the trivalent oral vaccination against poliomyelitis may be favourably compared with the mass dusting with insecticides in control of epidemic typhus. And from the standpoint of cost, which is always an important consideration for the public health administrator, trivalent oral vaccinations should certainly make smaller demands on our resources.

Summary

The serological and clinical responses of 526 children who were given the three sero-types of attenuated poliovirus as an oral vaccine are described, and reference is made to the clinical observations during eight additional trials comprising in all approximately 2,000 subjects ranging in age from 1 to 21 years. They represent a variety of field conditions in Cuba.

Clinical evidence of nervous or other disturbances attributable to the vaccine was not observed, and vaccination in the presence of acute infectious diseases such as mumps, rubella, and influenza, as well as in certain chronic diseases, was uneventful.

Conversion rates for sero-negatives to positives varied for the three types of poliovirus and in the six trial groups; the overall rate for the study was 88%. In addition, booster responses were shown by children whose pre-feeding titres were between 1:4 and 1:512. The response rates in such children were 36% for type I poliovirus, 45% for type II, and 62% for type III.

The high rates of response when all three strains of poliovirus were administered simultaneously is a finding of considerable practical importance, and its implications are discussed.

We gratefully acknowledge the co-operation of Drs. Carlos Hernandez Miyares, Alvaro Silva, Maria Oliva Barreiro, and Daniel Alonso, who did the clinical follow-up of the subjects comprising the different groups included in this study.

REFERENCES

Cox, H. R., Cabasso, V. J., Markham, F. S., Moyer, A. W., Moses, M. J., Roca-Garcia, M., and Ruegsegger, J. M. (1960). To be published.

Koprowski, H., Jervis, G. A., and Norton, T. W. (1952). *Amer. J. Hyg.*, **55**, 108.

Pan American Sanitary Bureau (1958a). Scientific Publications, No. 38.

—— (1958b). Ibid., No. 40.

Paul, J. R., Melnick, J. L., and Riordan, J. T. (1952). *Amer. J. Hyg.*, **56**, 232.

Sabin, A. B. (1955). *Amer. J. med. Sci.*, **230**, 1.

There are 18,588 young men and women from the United Kingdom dependent territories studying in Britain and the Irish Republic compared with just over 4,000 ten years ago. More than one out of every three of the present students are nurses, of whom there are 6,365. Of the total number, 3,383 are studying at universities. After nursing, the most popular subject is law, which is the choice of 2,237 of the students. There are 1,814 G.C.E. students, and 1,297 are studying engineering and technology, 1,135 arts and economics, and 1,004 medicine and pharmacy.—(Colonial Office Information Department.)

ABO BLOOD GROUPS AND CANCER OF OESOPHAGUS, CANCER OF PANCREAS, AND PITUITARY ADENOMA

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It is a striking fact that up to the present time the diseases for which really strong evidence of associations with the ABO blood groups have emerged are, with one exception, conditions of, or associated with, the upper part of the gastro-intestinal tract. The one exception is Helmbold's (1958) finding of a highly significant excess of group A among women suffering from uterine cancers. Hence diseases of the gastro-intestinal tract not hitherto studied are of particular interest. Cancer of the pancreas and cancer of the oesophagus are diseases for which serious operation is often required, hence blood-grouping is frequently carried out and retrospective studies become possible. Neither condition is, however, common enough to make it easy to secure adequate numbers. The series reported in this paper are distinctly small, but it is hoped that other workers may be able to add further samples in due course.

The third disease, chromophobe adenoma of the pituitary, is also of particular interest because of the finding by Mayr, Diamond, Levine, and Mayr (1956) of a very marked excess of group O, which contrasted with the absence of any apparent blood-group association in other intracranial tumours. The further findings published by Damon (1957) weakened the evidence, but clearly a problem remained in regard to which the collection of further data was highly desirable.

We were further encouraged to investigate chromophobe adenoma of the pituitary gland when we recollected that this is not, strictly speaking, a brain tumour; the anterior pituitary from which chromophobe tumour grows develops from what is really pharyngeal epithelium, and the anterior pituitary is much more closely related to the epithelium of the salivary glands, whose tumours have shown an extremely strong ABO blood-group association (Cameron, 1958), than to the nerve cells of the brain.

Control Series

The control series used in the present paper are listed in Table I. The London sample is that of Discombe and Meyer (1952), which we have used before (Aird, Bentall, Mehigan, and Roberts, 1954). The Oxford sample was provided by the Nuffield Blood Group Centre of the Royal Anthropological Institute, and has also been used before (McConnell, Pyke, and Roberts, 1956). All the other series have kindly been provided by the Nuffield Blood Group Centre and are based on consecutive registrations of new donors by the National Blood Transfusion Service. Those for Birmingham, Cardiff, Liverpool, and Sheffield are enlarged samples which include the smaller numbers used on previous occasions. At five centres, however—namely, Bristol, Manchester, Newcastle, Glasgow, and Leeds—entirely new samples have been substituted for those previously used. We have done this deliberately, as it serves to emphasize an important point in the selection of population controls.

Some writers have been concerned over the choice of population controls and the supposed errors or discrepancies to which they might lead. Manuila (1958) is especially critical in this respect. Some detailed comments on his contentions have been made in a recent paper (Roberts, 1959a). One important point is that successive rationally selected samples from the same areas show no more fluctuation of frequencies from one to another than would be expected by chance, and this is allowed for in estimating significance. At the Nuffield Blood Group Centre some hundreds of thousands of consecutively registered blood donors have been counted and successive samples from the same areas repeatedly compared. The differences have turned out to be extremely close to those theoretically expected (A. C. Kopec, 1959, personal communication). Essentially the same conclusions are reached by Buckwalter and Knowler (1958), who have carried out a detailed analysis on control samples in Iowa amounting to 50,000 individuals. The one series which did yield significant discrepancies was the professional blood donors, who differed from the others in being higher in group O. This is not surprising, as usefulness is likely to be a factor in such a specially selected or self-selected group.

At the five centres specially mentioned above, the new samples are totally different from the old, and a comparison of the figures is given in Table II. The percentage frequencies are closely similar in each instance. The only differences which even approach significance at the 5% level are the distributions for the AB's at Bristol

TABLE I.—*Control Samples*

Centre	O	A	B	AB	Total
London ..	4,578	4,219	890	313	10,000
Oxford ..	2,888	2,839	557	208	6,492
Birmingham ..	4,559	4,038	751	242	9,590
Bristol	861	905	164	59	1,989
Cardiff ..	403	357	86	28	874
Liverpool ..	4,124	3,131	736	211	8,202
Manchester ..	2,570	2,221	490	150	5,431
Sheffield ..	1,837	1,709	324	132	4,002
Leeds	2,966	2,582	515	197	6,260
Newcastle ..	1,971	1,532	388	141	4,032
Glasgow ..	3,150	1,911	667	200	5,928

TABLE II.—*Comparison of Alternative Control Samples from the Same Centres*

Centre	Sample	No.	Percentage Frequencies			
			O	A	B	AB
Bristol	Present	1,989	43·3	45·5	8·2	3·0
	Previous	*40,740*	*44·0*	*44·1*	*8·2*	*3·6*
Manchester	Present	5,431	47·3	40·9	9·0	2·8
	Previous	*9,370*	*48·4*	*40·3*	*8·4*	*2·9*
Newcastle	Present	4,032	48·9	38·0	9·6	3·5
	Previous	*13,572*	*48·6*	*38·8*	*9·7*	*2·9*
Glasgow	Present	5,928	53·1	32·2	11·3	3·4
	Previous	*5,898*	*53·9*	*32·3*	*10·8*	*3·0*
Leeds*	Present	5,548	53·5	46·5	—	—
	Previous	*21,164*	*53·7*	*46·3*	—	—

*O and A only

and Newcastle. AB's are essentially irrelevant to the comparisons in this paper, and, in any event, the previous figure for Bristol was somewhat suspect. As already mentioned, all the new samples were provided by the Nuffield Blood Group Centre. The previous ones were obtained very differently. At Bristol the original count was made on blood donors during the early part of the war (Roberts, 1948). Similarity to the Nuffield Centre frequencies is all the more remarkable because the previous groupings were known to include a not inappreciable proportion of errors, as described in the paper quoted. At that time it was the practice to group donors, often in the field, on registration, and to correct these as necessary when donations of blood were made. This practice was soon afterwards abandoned. At Manchester the previous series is a very good one given by Stratton (1953), but it refers to the Manchester hospital area instead of the city, as is the case with the new series. At Glasgow and Leeds the samples were different, and at Leeds, as at Bristol, the first samples were based on wartime groupings, and so were obtained many years before the new sample.

We have emphasized the correspondences because they indicate very clearly that rationally selected control population samples for given areas turn out to give closely similar results. The differences between them are trivial in comparison with those found in connexion with proved blood-group and disease associations; for, of course, it is only relatively very large associations that can be detected with samples of practicable size.

Carcinoma of the Pancreas

At the various centres listed all cases of cancer of the pancreas that had been blood-grouped were included. It is possible that some of these may have been carcinomas of the ampulla of Vater or of the lower end of the common bile-duct, for when these are advanced and have spread into the pancreas it is not always possible to distinguish their precise anatomical origin. The basic data are given in Table III.

With such small numbers it does not seem worth while complicating the table with subdivisions by age and sex. These have been recorded, however, and may be used on a further occasion. Table IV shows the findings in briefest summary. The control frequencies are simply weighted according to the number of patients at each centre. The comparison is given for illustration only, and, of course, no statistical tests can be carried out on these figures.

TABLE III.—*Cancer of Pancreas. Basic Data*

Centre	O	A	B	AB	Total
London	39	56	10	4	109
Birmingham	24	22	6	1	53
Bristol	21	26	5	2	54
Cardiff	17	21	4	1	43
Liverpool	58	67	4	4	133
Manchester	43	30	2	3	78
Sheffield	5	18	3	0	26
Leeds	11	8	3	0	22
Newcastle	17	18	5	0	40
Glasgow	37	19	5	1	62
Total	272	285	47	16	620

TABLE IV.—*Cancer of Pancreas. Brief Summary*

Blood Group	Cancer of Pancreas	Controls*	Increase or Decrease on Controls
O	43·9%	47·9%	−8·4%
A	46·0%	40·1%	+14·7%
B	7·6%	9·1%	−16·5%
AB	2·6%	3·0%	—

* Controls weighted according to number of patients at each centre.

The method we now use for the combination of data from different centres is that of Woolf (1955), which is particularly appropriate for the purpose. This method has the advantage that the results appear in a form with a simple and direct physical meaning, with the further advantage that centres with distinctly different ABO frequencies in their populations can be combined without introducing bias.

In Table V the figures shown in the columns giving relative incidences are obtained by simple cross-multiplication. Thus, for example, the results for London show 39 O's and 56 A's among patients with cancer of the pancreas, as against 4,578 O's and 4,219 A's amongst the controls.

$$\frac{(56 \times 4{,}578)}{(39 \times 4{,}219)} = 1.56$$

So we can say that this sample indicates an incidence of the disease of 1.56 in persons of group A as compared with 1.0 in persons of group O. As regards the O and A comparison, it will be seen that at three centres—London, Liverpool, and Sheffield—the departure from unity is significant at the 5% level. At four centres there is a non-significant excess of A, but at three—Manchester, Leeds, and Glasgow—group O is in excess. The combination of these data yields an average weighted relative incidence of 1.25 in group A as against 1.0 in group O. χ^2 for the deviation from unity, with 1 degree of freedom, is 6.57, corresponding to a probability of a little more than 1 in 100. Table IV shows that the reduction in group B as against the controls is even greater than that on group O. Accordingly the last two columns of Table V give a comparison of the incidence in group A relative to that in groups O and B combined. The significance of the difference from unity is somewhat increased, the χ^2 of 8.36 corresponding to a probability of about 1 in 250. For both comparisons the differences between centres do not exceed those to be expected by chance.

TABLE V.—*Cancer of Pancreas. Incidence in Group A Relative to Incidence in Group O and in Groups (O+B)*

Centre	Relative Incidence A:O	χ^2	Relative Incidence A:(O+B)	χ^2
London	1·56	4·47	1·48	3·99
Birmingham	1·03	0·01	0·96	0·02
Bristol	1·18	0·30	1·13	0·20
Cardiff	1·39	0·99	1·37	0·99
Liverpool	1·52	5·38	1·68	8·47
Manchester	0·81	0·80	0·92	0·13
Sheffield	3·87	7·13	2·85	6·02
Leeds	0·84	0·15	0·77	0·35
Newcastle	1·36	0·83	1·26	0·52
Glasgow	0·85	0·35	0·90	0·13
Mean weighted relative incidence	1·25		1·27	
χ^2 Total		20·41		20·82
χ^2 Diff. from unity. D. of F.=1		6·57		8·36
χ^2 Heterogeneity. D. of F.=9		13·84		12·46
P Heterogeneity		0·13		0·2

There is evidence of some strength that cancer of the pancreas is commoner in persons of group A than in persons of groups O or B. But we should not like to attach too much weight to this result, and hope that other series will be forthcoming, which will disprove, or prove beyond reasonable doubt, the reality of this association. But at least the present evidence is rather

more than suggestive. If it is ultimately confirmed, this is a highly interesting finding because of the known relationship between diabetes and carcinoma of the pancreas. It has long been known that carcinoma of the pancreas is commoner in diabetics than in non-diabetics, and it has appeared that blood group A is possibly commoner in diabetics than in the general population. The association between group A, diabetes, and carcinoma of the pancreas strongly suggests an analogy with the association of blood group A with pernicious anaemia and with carcinoma of the stomach, for it is known that carcinoma of the stomach is commoner in patients who suffer from pernicious anaemia than in population controls.

In this connexion Buchanan and Higley (1921) reported an examination of the ABO blood groups of patients with jaundice at the Mayo clinic. This group of jaundiced patients showed an excess of A, which Buchanan and Higley regarded as unimportant but which, when statistically analysed, shows a significant excess of group A. Buchanan and Higley separated from the figures for jaundice a series of patients who suffered from gall-stones, so that the jaundice series would in all probability include a greater number of carcinoma of the pancreas. The excess of A in the jaundice group may have reflected a number of cases of carcinoma of the pancreas in the jaundice series.

Carcinoma of the Oesophagus

This series was restricted to carcinomas of the oesophagus which were known to have been squamous in type; it was thought that this restriction would prevent the inclusion of any carcinomas of the stomach spreading up to the lower part of the oesophagus. These would presumably be glandular.

TABLE VI.—*Cancer of Oesophagus. Basic Data*

Centre	O	A	B	AB	Total
London	58	61	15	3	137
Birmingham	28	33	7	1	69
Bristol	10	13	2	1	26
Cardiff	24	17	5	2	48
Liverpool	68	64	10	3	145
Manchester	27	20	3	1	51
Sheffield	7	10	4	0	21
Leeds	15	16	3	3	37
Newcastle	12	8	3	1	24
Glasgow	25	18	8	1	52
Total	274	260	60	16	610

TABLE VII.—*Cancer of Oesophagus. Brief Summary*

Blood Group	Cancer of Oesophagus	Controls*	Increase or Decrease on Controls
O	44·9%	47·9%	−6·3%
A	42·6%	40·1%	+6·2%
B	9·8%	9·0%	+8·9%
AB	2·6%	2·9%	—

* Controls weighted according to number of patients at each centre.

The basic data are shown in Table VI, and a brief summary is given in Table VII. The detailed comparison which is shown in Table VIII indicates an average relative incidence of the disease of 1.14 in persons of group A as compared with 1.0 in persons of group O. χ^2 for the difference from unity is only 2.17, so it is not significant at the 5% level. Actually the observed figure is compatible with the null hypothesis that there is no association; but it is equally compatible with a true incidence of 1.2, which represents the very highly significant excess on the large numbers of cancer of the stomach so far published.

TABLE VIII.—*Cancer of Oesophagus. Incidence in Group A Relative to Incidence in Group O*

Centre	Relative Incidence A:O	χ^2
London	1·14	0·51
Birmingham	1·33	1·23
Bristol	1·24	0·25
Cardiff	0·80	0·47
Liverpool	1·24	1·49
Manchester	0·86	0·27
Sheffield	1·54	0·75
Leeds	1·23	0·32
Newcastle	0·86	0·11
Glasgow	1·19	0·30
Mean weighted relative incidence	1·14	
χ^2 Total		5·70
χ^2 Diff. from unity. D. of F. = 1		2·17
χ^2 Heterogeneity. D. of F. = 9		3·53
P Heterogeneity		0·9

One other series has been recorded. Billington (1957) reports the following series from Sydney: O, 50; A, 54; B, 12; AB, 3, against control frequencies of O, 14,672; A, 11,514; B, 2,912; AB, 902. χ^2 for the O:A comparison is 2.64. If his figures are added to those of Table VIII the total χ^2 for the deviation from unity becomes 4.03, and so is just significant at the 5% level. The areas, adding his material, are still perfectly homogeneous. Hence there is already some slight indication that cancer of the oesophagus may ultimately prove similar to cancer of the stomach in showing an increased incidence in persons belonging to group A. It is also emphasized once again how large numbers must be in studies of this kind. A series of 600 patients is quite inadequate for detecting even a moderately large association; the counts needed are to be numbered in thousands rather than hundreds, and we trust that further results will be forthcoming.

Adenoma of the Pituitary

Mayr *et al.* (1956) recorded the ABO blood-group frequencies of 367 patients with brain tumours of various kinds. With the exception of 123 with pituitary adenomata, the figures were unremarkable. But for the pituitary tumours the figures were O, 74; A, 24; B, 19; AB, 6. The excess of group O and deficiency of group A were thus truly striking and very highly significant. Later, Damon (1957) published a further series from New York, but, though he still found some excess of O, the association was very much smaller (151 whites gave an O:A ratio of 1.33 and 34 negroes 1.35). Our own series consists of 408 patients with pituitary adenomata drawn from seven centres. The basic data are shown in Table IX; a brief summary is given in Table X and a detailed analysis in Table XI.

It will be seen from Table X that the overall differences between the patients and the control series are

TABLE IX.—*Chromophobe Adenoma of Pituitary. Basic Data*

Centre	O	A	B	AB	Total
London	80	67	18	6	171
Oxford	36	40	4	2	82
Birmingham	15	9	1	0	25
Bristol	10	11	3	0	24
Cardiff	11	10	3	1	25
Liverpool	15	19	3	0	37
Manchester	26	12	6	0	44
Total	193	168	38	9	408

TABLE X.—*Chromophobe Adenoma of Pituitary. Brief Summary*

Blood Group	Adenoma	Controls*
O	47·3%	46·1%
A	41·2%	42·1%
B	9·3%	8·8%
AB	2·2%	3·0%

* Controls weighted according to number of patients at each centre.

TABLE XI.—*Chromophobe Adenoma of Pituitary. Incidence in Group O Relative to Incidence in Group A*

Centre	Relative Incidence O : A	χ^2
London	1·10	0·33
Oxford	0·88	0·28
Birmingham	1·48	0·85
Bristol	0·96	0·01
Cardiff	0·97	0·00
Liverpool	0·60	2·19
Manchester	1·87	3·21
Mean weighted relative incidence	1·04	
χ^2 Total		6·87
χ^2 Diff. from unity. D. of F. = 1		0·17
χ^2 Heterogeneity. D. of F. = 6		6·70
P Heterogeneity		0·4

negligible. The weighted mean relative incidence in group O as compared with group A is only 1.04, as shown in Table XI. Nor is there significant heterogeneity between centres. At an earlier stage, when figures were briefly reported (Roberts, 1959b), patients at Manchester gave the rather unusual figures—O, 22; A, 6—which led to a significant χ^2 at this centre. Further figures from Manchester, however, included 4 O's and 6 A's, so this suggestion of an excess of O at one centre, similar to that found by Mayr *et al.*, has been reduced to non-significance.

Rhesus Groupings

Fairly adequate numbers of groupings (positive and negative) are available for patients with carcinoma of the pancreas and carcinoma of the oesophagus. The results are shown in Table XII. With both diseases the proportion of rhesus-negatives is within the range to be expected in the general population of Great Britain.

TABLE XII.—*Rhesus Groupings*

	Rh+	Rh−	Total	% Rh−
Cancer of pancreas	416	82	498	16·5
,, ,, oesophagus	418	93	511	18·2

Summary

620 patients suffering from cancer of the pancreas show an excess of group A and a deficiency of groups O and B. The differences are moderately significant. The increased incidence in group A relative to group O corresponds to a probability of about 1 in 100, and in group A relative to groups O and B combined about 1 in 250.

610 patients suffering from cancer of the oesophagus show some excess of group A, but this is non-significant. On these numbers, however, the figures are not incompatible with an incidence in group A as high as that found in cancer of the stomach.

408 patients with adenomata of the pituitary gave ABO frequencies closely similar to those of the controls.

The proportion of rhesus-negatives among those with cancer of the pancreas and of the oesophagus is within the range expected in Great Britain.

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REFERENCES

Aird, I., Bentall, H. H., Mehigan, J. A., and Roberts, J. A. F. (1954). *Brit. med. J.*, **2**, 315.

Billington, B. P. (1957). *Aust. Ann. Med.*, **6**, 56.

Buchanan, J. A., and Higley, E. T. (1921). *Brit. J. exp. Path.*, **2**, 247.

Buckwalter, J. A., and Knowler, L. A. (1958). *Amer. J. hum. Genet.*, **10**, 164.

Cameron, J. M. (1958). *Lancet*, **1**, 239.

Damon, A. (1957). *Science*, **126**, 452.

Discombe, G., and Meyer, H. (1952). *Amer. J. clin. Path.*, **22**, 543.

Helmbold, W. (1958). *Seventh Congress of the International Society of Blood Transfusion, Rome, 1958*, p. 34 (abstract).

McConnell, R. B., Pyke, D. A., and Roberts, J. A. F. (1956). *Brit. med. J.*, **1**, 772.

Manuila, A. (1958). *J. Amer. med. Ass.*, **167**, 2047.

Mayr, E., Diamond, L. K., Levine, R. P., and Mayr, M. (1956). *Science*, **124**, 932

Roberts, J. A. F. (1948). *Ann. Eugen. (Lond.)*, **14**, 109.

—— (1959a). *Brit. med. Bull.*, **15**, 129.

—— (1959b). *Proceedings 10th International Congress of Genetics, Montreal*, **1**, 120.

Stratton, F. (1953). In *Clinical Genetics*, edited by A. Sorsby, p. 480. Butterworth, London.

Woolf, B. (1955). *Ann. hum. Genet.*, **19**, 251.

This spring the British Council has 33 exhibitions of British books touring 26 countries. They total 23,779 volumes. Ten exhibitions are in Europe, nine in Asia, six in Latin America, seven in Africa, and one in Australia. Their titles cover subjects ranging from science, medicine, and economics to printing, social services, and sailing. Six exhibitions, at present in Norway, Italy, Malaya, Iran, Sudan, and Peru, are on the teaching of English. Scientific book exhibitions are being circulated in Sweden, India, Burma, and Indonesia. Among 10 more in preparation are exhibitions of books on science, technology, and medicine for Japan, on general education and the teaching of English for Vietnam, and of publications from British university presses for West Germany. The majority of British Council book exhibitions are prepared for specific countries and the books remain in that country after the tour. They are assembled in London.

BLOOD GROUPS OF GASTRIC ULCER AND CARCINOMA

BY

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The earliest attempt to find a relationship between the ABO blood groups and disease was that of Alexander (1921). From a study of 50 malignant neoplasms he concluded that groups B and AB were peculiarly susceptible to various forms of neoplasm and that O was more stable or resistant, but admitted that his figures were too small for the susceptibility of group A to be discerned. He found that neoplasms in B and AB groups were severe and rapidly growing, while those in groups O and A were of low malignancy and of long duration.

In the same year Buchanan and Higley (1921) published their results of the ABO groups in 2,446 patients. Their conclusions were that there was no relationship between blood groups and any disease; that the percentage distribution of blood groups shown originally by Moss, whom they quoted, was approximate and capable of a considerable variation, which did not have any special significance; and that nationality should be considered in any statistical study of blood groups. Yet their figures show an excess of group O in chronic ulcers (148 peptic out of 172) and an excess of group A in pernicious anaemia and jaundice.

Another early report on blood groups and disease was that of Johannsen (1925) from Copenhagen. Basing his conclusions on a series of 263 various malignant tumours and 107 carcinomata of the uterus, he claimed that A and AB individuals were more susceptible and B and O relatively more resistant to the external influences that provoke carcinoma.

Mitra (1933) attempted to discover if the ABO groups had any influence on certain pathological states. He concluded, as the result of examining groups from a very heterogeneous series of diseases, that there was none, except in helminthiasis (112 cases) where group AB was preponderant, and in malignancy (16 cases) where A was diminished and AB increased.

In a series of 461 cases of widely differing types of neoplasm Macleod (1937) found no ABO relationship, but concluded that, in 193 cases diagnosed as pernicious anaemia, groups B and AB showed a high percentage (12.95 and 6.7 respectively). Goldfeder and Fershing (1937) cited five series in the literature: Hoche and Moritsch (1926) found a slight increase in A and AB in patients with malignant disease; Hirschfeld and Hittmair (1926) did not demonstrate any variation from the normal range in 150 cancer patients; Einaudi (1927) showed no variation from normal in his series; Thomsen (1931) concluded that there were no definite differences from normal in 1,200 cancer cases; Matousek (1935), from a study of 200 women with malignant tumours, claimed an excess of group O in carcinoma of the breast. Goldfeder and Fershing themselves determined the groups in 300 cases of cancer of 44 different sites and showed a diminished A and an increased B and AB, but said, significantly, that whether these results were valid would depend on the study of larger numbers. Ugelli (1936) made the important discovery that in his series of 244 peptic ulcers there was an excess of group O when compared with a population sample, but Tinney and Watkins (1941), who ascertained the ABO groups in 612 various blood dyscrasias, stated that they did not believe there was any relationship between an individual group and any specific haematological disease. Lessa and Alarcao (1949), confirmed the results of Ugelli with 500 of their own cases of peptic ulcer.

The first report which based its conclusions on large numbers was that of Aird, Bentall, and Fraser Roberts (1953). Initially, the experiment was designed to discover if there was a connexion between the higher incidence of carcinoma of the stomach in Northern England and genetical differences that are shown by a higher incidence of group O in the north and of group A in the south. They investigated the blood groups of 1,046 cases of stomach cancer in the North of England, 1,340 in London, and 478 in Scotland, and in all the hospitals concerned there was an excess of group A and a deficiency of group O.

Statistical calculations from all the hospital figures showed the excess of group A to be highly significant. The same authors also quoted the blood-group distribution of 704 cases of gastric cancer from Basle, and among these, too, there was a distinctly significant excess of group A.

However, in the same month in which the report of Aird *et al.* (1953) appeared, Mayo and Ferguson (1953) produced their results of the ABO groups in various gastro-intestinal diseases, which included 935 cases of carcinoma, and concluded that there was no significant relationship between the disease studied and the groups.

In 1954 Aird, Bentall, Mehigan, and Fraser Roberts produced the results of a further investigation into the relationship between blood groups and disease, and the most interesting finding was a statistically significant association between group O and peptic ulcer. They found no great variation from controls in the blood groups in cancer of breast, bronchus, and colon and rectum. A total of 1,015 patients with gastric and 1,851 with duodenal ulcers had their blood groups analysed and no difference in the incidence of the ABO groups between the two ulcers was observed.

A Diversity of Findings

Since the publications of Aird *et al.* (1953, 1954) a number of other investigations have been reported, some with confirmatory results and others with conflicting results. Køster, Sindrup, and Seele (1955), in Denmark; Buckwalter, Wohlwend, Colter, Tidrick, and Knowler (1956a), in America; and Segi, Fujisaku, Kurihara, and Moniwa (1957), in Japan, found a significant excess of group A in carcinoma of the stomach. From his results, Jordal (1956), in Denmark, claimed a significant excess of A (his probability value was 6%), and Weiser (1957), in Germany, found a slight excess of A. Mayr, Diamond, Levine, and Mayr (1956), in America, and Jennings, Balme, and Richardson (1956), and Walther, Raeburn, and Case (1956), in England, showed an excess of A.

On the other hand, Wallace (1954), in Scotland, found no significant increase in group A in gastric carcinoma; neither did Billington (1956a, 1956b), in Australia, nor Speiser (1956), in Vienna.

Similarly, the findings of Aird *et al.* for gastric ulcer have been followed by a diversity of results. Køster

et al. (1955), Heistø (1956), and Buckwalter *et al.* (1956b) agreed, but Clarke (1955), Clarke, Cowan, Wyn Edwards, Howel-Evans, McConnell, Woodrow, and Sheppard (1955), Billington (1956a), and Brown, Melrose, and Wallace (1956) found no significant difference between controls and patients with gastric ulcer.

Jennings *et al.* (1956) classified 119 cases of carcinoma of the stomach into three sites: (1) pyloric and antral, (2) cardiac, and (3) body, and found that the overall excess of group A in carcinoma of the stomach was due to the excess of that group in pyloric lesions. They found no association between blood groups and lesions elsewhere in the stomach. Later in the same year, Billington (1956b), from a series of 483 carcinomata, confirmed the significant excess of group A in pyloric lesions, and also showed that in cardiac lesions there was an excess of group A, and in body neoplasms group O was preponderant. However, Haddock and McConnell (1956) did not confirm the findings of these authors, and, on the contrary, showed an association between A and body and cardiac cancers, and between O and pyloric cancers.

Billington (1956a), in another paper, showed that there was an increased incidence of A in prepyloric chronic gastric ulcer and an excess of O in non-pyloric ulcers. Balme and Jennings (1957) compared sites and ABO groups of both gastric ulcers and cancers, and reported that the A/A+O ratio was similar for both lesions at each site. They found that in antral lesions (male and female) A was more frequent, and in the body lesions O was more frequent, but only in males. The explanation of the association between A and cancer was because most cancers were antral in site, whilst the association between O and gastric ulcer was due to the fact that most ulcers occurred in the body.

Most of the reports on the ABO distribution in gastric ulcer and gastric carcinoma were collected, combined, and statistically examined by Fraser Roberts (1957). With the mathematical technique of Woolf (1955) it is possible to combine the various authors' series. It will be recalled that a statistically significant excess of group A in gastric cancer was not claimed by all investigators, yet when all the series were combined (Aird *et al.*, 1953; Walther *et al.*, 1956; Wallace, 1954; Køster *et al.*, 1955; Speiser, 1956; Buckwalter *et al.*, 1956a; Billington, 1956b; Hollander, quoted by Aird *et al.*, 1953) it was shown by Fraser Roberts (1957) that there was an overall association with group A, and that the centres were not significantly heterogeneous. Using the same method, he demonstrated an excess of O in patients with gastric ulcers, from series quoted by Aird *et al.* (1954), Clarke *et al.* (1955), Køster *et al.* (1955), Brown *et al.* (1956), Heistø (1956), Speiser (1956), Buckwalter *et al.* (1956b). The centres showed no significant heterogeneity for gastric ulcer.

This paper reports the findings of an investigation into the relationship of blood groups and gastric ulcer and cancer in Glamorganshire and Monmouthshire.

Methods

Gastric Cancer.—The in-patient records from a number of hospitals were examined to find cases of carcinoma of the stomach and their blood groups. From the operation, pathology, and post-mortem reports the site of the lesion was determined. The pyloric region was accepted as the distal 1 in. (2.5 cm.) of the stomach; "body region" means that the pyloric region and cardiac region were not involved; "cardiac region" indicates involvement of the cardiac orifice and the adjacent part of the stomach and oesophagus. "Extensive" means that the lesion could not be allotted to a particular region and includes cases of linitis plastica. No case of squamous carcinoma has been included.

Gastric Ulcer.—From the same hospitals cases of gastric ulcer diagnosed at operation, radiologically, gastroscopically, and at post-mortem examination were obtained. The ulcers found at operation and necropsy were placed in one of two sites, pyloric or non-pyloric.

TABLE I.—*Control Figures*

Area	O	A	B	AB	Total
Glamorgan 1 ..	1,658 47·18%	1,356 38·59%	373 10·61	127 3·61%	3,514
,, 2 ..	1,025 44·53%	979 42·53%	206 8·95%	92 4%	2,302
Monmouthshire	986 43·47%	988 43·56%	206 9·08%	88 3·88%	2,268

Controls (see Table I).—The ABO blood-group distributions for Glamorganshire and Monmouthshire were given me by Dr. A. C. Kopec. In her accompanying letter she pointed out that Glamorganshire could be divided into two areas, each with a different ABO blood-group distribution, and the difference was statistically significant. Area 1 comprised Cardiff, Swansea, and all of Glamorganshire except the north-eastern corner. This north-eastern corner (area 2) is an area within a line joining Dowlais, Merthyr, Aberdare, Treorchy, Pontyclun, and Caerphilly, and the eastern border of the county. The ABO blood-group distribution in Monmouthshire shows no statistical differences from that of Glamorganshire area 2. According to their addresses, patients were assigned to one of the Glamorganshire areas or Monmouthshire.

Statistical Methods.—The statistical method employed in the comparison of the ABO groups of the disease with those of the population was that of Woolf (1955), which was also used by Fraser Roberts (1957) in a statistical survey of various reports. The comparison of the ABO groups of one site in the stomach with those of another was made using the 2×2 Table with Yates's corrections if numbers were less than 100. The value of P taken as the significant level was 0.05.

Blood Groups.—The blood groups of nearly all of these patients were determined in the laboratories of the hospitals, using the tube technique. In a small number in which it was a matter of urgency the tile technique was employed. In no case was the blood group assumed to be group O just because the patient was given an emergency group O transfusion. In some cases the group was determined in the laboratories of the National Blood Transfusion Service of the Welsh, or South-Western, Regional Hospital Boards.

Disease and Population

Gastric Cancer

A total of 780 cases of gastric carcinoma was obtained by examining the case records in a number of hospitals. Of these there was histological confirmation in 610, and in the remainder the diagnosis was made by macroscopic appearances (Table II).

TABLE II.—*Blood Groups of Gastric Cancer*

Method of Diagnosis	O	A	B	AB	Total
Histological ..	255 41·8%	283 46·4%	56 9·18%	16 2·62%	610
Macroscopic ..	71 41·77%	79 46·47%	15 8·82%	5 2·94%	170
Total ..	326	362	71	21	780

$\chi^2 = 0.0062$; P = approximately 1.

TABLE III.—*Cases of Gastric Cancer According to the Geographical Area in Which the Patient Lived*

Area	O	A	B	AB	Total
Glamorgan 1 ..	152 44·06%	157 45·51%	29 8·41%	7 2·03%	345
,, 2 ..	63 44·68%	61 43·26%	13 9·22%	4 2·84%	141
Monmouthshire	96 36·93%	132 50·77%	23 8·85%	9 3·46%	260
Combined Glamorgan 2 and Monmouthshire ..	159 39·66%	193 48·14%	36 8·98%	13 3·24%	401

TABLE IV.—*Analysis of Gastric Carcinoma*

Areas		Total in Disease Series	Relative Incidence A : O	χ^2
Glamorgan 1 ..		345	1·263	3·820
,, 2 and Monmouthshire ..		401	1·241	3·738
Total		746		
Mean weighted relative incidence ..			1·251	
χ^2	Total			7·558
	Difference from unity. D. of F. = 1			7·548
	Heterogeneity			0·010
P	Heterogeneity			1·0

TABLE V.—*Blood Groups of Gastric Ulcer*

Method of Diagnosis	O	A	B	AB	Total
Histologically proved ulcer	372 53·92%	254 36·81%	49 7·10%	15 2·17%	690
Gastroscopical, radiological, etc.	154 48·73%	131 41·46%	29 9·18%	2 0·63%	316
Total ..	526	385	78	17	1,006

$\chi^2 = 2.329$; P = 0·13.

TABLE VI.—*Cases of Gastric Ulcer, All Diagnostic Types, According to Geographical Areas in Which the Patients Lived*

Area	O	A	B	AB	Total
Glamorgan 1 ..	289 52·93%	207 37·91%	44 8·06%	6 1·1%	546
,, 2 ..	57 50·9%	46 41·08%	6 5·35%	3 2·68%	112
Monmouthshire	163 51·1%	123 38·56%	26 8·15%	7 2·19%	319
Combined Glamorgan 2 and Monmouthshire ..	220 51·04%	169 39·21%	32 7·42%	10 2·32%	431

TABLE VII.—*Analysis of Incidence of All Gastric Ulcers*

Area		Total in Disease Series	Relative Incidence O : A	χ^2
Glamorgan 1 ..		546	1·141	1·82
,, 2 and Monmouthshire		431	1·274	5·08
Total ..		977		
Mean weighted relative incidence ..			1·199	
χ^2	Total			6·90
	Difference from unity. D. of F. = 1			5·032
	Heterogeneity			1·868
P	Heterogeneity			0·168

As there is no significant difference in the A and O groups between the histologically proved and macroscopically diagnosed cases, both are included in all statistical comparisons.

Table III shows the distribution of the patients with carcinoma of the stomach in Monmouthshire and the two areas of Glamorganshire. The remaining 34 patients resided outside these counties and are excluded from the analysis of population and disease.

In Table IV is the statistical comparison of the blood groups of the disease with the controls. The χ^2 result is almost significant in the two geographical areas analysed, but if the two areas are taken together the χ^2 result is significant ($\chi^2 = 7.548$; P = 0.0062) and the areas are homogeneous. Therefore in Glamorgan and Monmouthshire there is a statistically significant relationship between group A and carcinoma of the stomach.

Gastric Ulcer

From the same hospitals 690 cases of histologically proved chronic gastric ulcers were obtained and also 316 diagnosed by gastroscope, radiological examination, and at operation and necropsy but without histological proof (Table V). There is no significant difference between these two diagnostic divisions, and both types are included in the statistical analysis.

These cases were then, according to the address of the patient, assigned to one of three geographical areas as described for carcinoma of the stomach (Table VI). Twenty-nine patients resided outside these areas and are not included in the analysis (Table VII).

There is no significant association between group O and gastric ulcer in Glamorgan 1, but there is a significant association in the Combined Glamorgan 2 and Monmouthshire. When the two areas are taken together the analysis reveals a significant relationship between O and gastric ulcer ($\chi^2 = 5.032$; P = 0.025) and the two areas are homogeneous (Table VII).

Relationship of Site of Lesion to Blood Group

Gastric Carcinoma.—From the operation, pathology, or post-mortem reports a note was made of the site of the lesion. This series also includes 140 cases from two Bristol hospitals (Table VIII). In each of the three sites and in the extensive and the not-sited classifications group A is in excess. The results in Table IX do not reveal any significant differences in the blood-group distribution between the various sites in the stomach.

TABLE VIII.—*Blood Groups and Sites of Cancer*

Site	O	A	B	AB	Total
Pylorus ..	144 42·86%	149 44·35%	31 9·23%	12 3·57%	336
Body	142 42·78%	154 46·38%	32 9·64%	4 1·21%	332
Cardiac ..	34 40·00%	46 54·21%	5 5·88%	—	85
Extensive ..	50 39·68%	62 49·21%	8 6·35%	6 4·76%	126
Not sited ..	17	23	—	1	41
Total ..	387 42·02%	434 47·12%	76 8·36%	23 2·50%	920

TABLE IX.—*Comparison of ABO Groups at the Various Sites of Gastric Cancer*

Comparisons	χ^2	P
Pyloric and body sites	0·083	0·78
Body and cardiac ,, ...	0·55	0·46
Pyloric ,, ,, ,, ...	0·86	0·35

TABLE X.—*Sites of Gastric Ulcer. Histologically Proved*

Sites	O	A	B	AB	Total
Pyloric ..	76 60·32%	37 29·36%	9 7·14%	4 3·18%	126
Non-pyloric ..	281 52·72%	204 37·9%	39 7·32%	11 2·06%	535
Total ..	357 54·01%	241 36·46%	48 7·26%	15 2·27%	661

Gastric Ulcer.—The histologically proved ulcers were divided, according to site, into pyloric and non-pyloric. The site was not known in some cases (Table X). Comparing the O and A groups in pyloric and non-pyloric ulcers, $\chi^2=2.782$, $P=0.094$, which is not a significant result.

Discussion

General Relationship Between Disease and Group

The relationship of group A with gastric cancer and of group O with gastric ulcer, that Aird *et al.* (1953, 1954) first showed, and that Fraser Roberts (1957) demonstrated for a number of different geographical areas, has been confirmed for Eastern Glamorganshire and Monmouthshire. It must now be apparent that people of group A are more liable to develop a carcinoma of the stomach, and those of group O to develop a gastric ulcer.

Stocks (1950) showed that the mortality of gastric cancer is positively correlated with the proportion of unskilled workmen in the population. But in a survey of the North of England, Fraser Roberts (1953) showed that there was no relationship between social status and ABO blood groups, nor between sex and the ABO blood groups. The relationship, therefore, of group A to cancer of the stomach is a general one amongst the population, and it cannot be explained on the basis of an association between blood groups and social status or sex.

An explanation of the association between these two diseases and the A and O groups has been sought in the relationship of acid production to blood groups. Køster *et al.* (1955) and Mosbech and Hauze (1956) found an association between group A and achlorhydria, but Brown *et al.* (1956) and Buckwalter *et al.* (1956a, 1957) found none. These results do not help to explain the association between gastric cancer and group A, and between gastric ulcer and group O.

Woolf (1955) demonstrated a hereditable component in cancer of the stomach, finding that actual deaths due to gastric cancer in relatives were greater than expected. There were, he considered, genetic and non-genetic factors, but the effect of the genetic factor was small compared with the non-genetic or exogenous factor. A study of cancer in twins was published by Gorer in 1938. While genetic factors, he claimed, did not play a decisive part in the development of tumours, his studies suggested that they play a major part in determining the organ affected by the tumour. This was especially true for carcinoma of the stomach. Videbaek and Mosbech (1954) investigated the pedigree of 332 patients with gastric cancer, and concluded that there was an inherited predisposition to gastric cancer, and it was not associated with a general disposition to cancer. These authors also said that unknown exogenous factors may accelerate its development. This opinion was confirmed by Macklin (1955), who wrote: "The inevitable conclusion is that genetic factors play the predominant role in gastric and intestinal cancer." He did not preclude the possibility that extrinsic factors played a part also.

The evidence, then, is in favour of there being a hereditary factor in the aetiology of gastric cancer. Perhaps the association between this disease and blood group A, which is inherited, explains the hereditary factor that others have observed.

Another hereditary factor that may be involved in the aetiology of gastric cancer and gastric ulcer is the secretor status of a person. It is genetically determined by a single pair of allelic genes independent of those for the ABO groups. About 75% of persons secrete the ABO group substance (A and H secreted in a group A secretor, B and H secreted in a group B secretor, AB and H in group AB secretor, and H in group O secretor) in saliva and gastric juice. Complicating this is the presence of a further blood-group-specific substance Le^a, which is found in the secretion of 90% of people independent of whether they are ABH secretors or non-secretors. The secretion of the Le^a substance is dependent upon another independent gene. The need to elucidate the secretory status so far as cancer of the stomach is concerned is emphasized by the finding of an excess of blood group A in tumours of salivary tissue (Cameron, 1958). There are therefore two sources of secretor substance (salivary glands and stomach) in the tumours of which there is an excess of group A.

Sheppard (1953) wondered whether the swallowing of secretor substance by group A secretors played a part in the inducement of gastric cancer. He thought that a reasonable explanation of the excess of group A in gastric cancer was that the stomach could be affected by an accumulation within it of saliva containing A substance. Jordal (1956) ascertained the secretor status in 492 patients with gastric cancer, gastric and duodenal ulcer, carcinoma of colon and rectum, and gall-stones. He claimed a statistically lower frequency of non-secretors in the whole series, but his figures for each disease were too small for an accurate conclusion to be drawn. McConnell and Sheppard (1957) assessed the secretory activity in 86 cases of gastric cancer, and concluded that, in 65 men, the percentage of non-secretors did not deviate significantly from normal. In 21 females they found 9.5% non-secretors, but added that their number was too small for any significance to be attached to the result.

Barber and Dunsford (1959) reported a case of gastric cancer, and in the serum of the patient there was an excess of group A substance. It was believed, because her cells were Le (a−b+), she was a secretor of A substance. In 12 other cases of presumed gastric cancer they found that there was no excess of A, B, or H substance, and in only one of 500 group A donors did they find a comparable amount of A substance. This result may be compared with that of Glynn, Holborow, and Johnson (1957), who found A substance in the cells of a gastric carcinoma and its metastases.

The result of investigations into the secretor status of gastric and duodenal ulcers was reported by Clarke, Evans, McConnell, and Sheppard (1959). They found, in Liverpool, that there was a clear association between ABH non-secretion and duodenal ulcers, but there was no association between gastric ulcers and non-secretion. Further, they showed a significant difference between these two ulcers when their ABH non-secretion was compared. Four years before, in 1955, these authors had shown an association between group O and

duodenal ulcer, but none between group O and gastric ulcer. They wondered, therefore, if in those areas where there was an association between group O and gastric ulcer there would also be an association between non-secretion and gastric ulcer.

Sites of Carcinoma of the Stomach

Billington (1956a, 1956b) showed a statistically significant excess of group A in carcinoma of both the pyloric and cardiac ends of the stomach, and an excess of group O in body cancers. Jennings *et al.* (1956) confirmed this significant excess of group A in pyloric cancers, but Haddock and McConnell (1956) showed a significant excess of group A in body cancers.

In this series of 920 gastric cancers the site was stated in 753 cases, but was considered so extensive in 126 that the site of the origin was not determinable. Group A was in excess, but not in numbers that were statistically significant when the sites were compared with each other, and group A was in excess, also, where the cancers were extensive and in those where no site was mentioned. These results therefore do not confirm the findings of previous investigators. Table XI shows the figures for these investigations and also the figures for this series.

TABLE XI.—*Sites of Gastric Cancer*

Series	Pylorus		Body		Cardia	
	O	A	O	A	O	A
Billington (1956b)	53	96	154	47	24	50
Jennings *et al.* (1956)	33	64	41	42	15	22
Present series ..	144	149	142	154	34	46
Haddock and McConnell (1956)	118	87	85*	109*		

* Body + cardia.

There are wide differences between this series and those of the other authors, and therefore I have not made an overall statistical comparison.

Balme (1956) endeavoured to explain the difference between his results and those of Haddock and McConnell (1956). He claimed that in 50% of his operation specimens the growth was so small that the diagnosis caused difficulty, but that, by being so small, the site was more accurately determinable. By the comparison of old with recent *x*-ray films, he said he was able to tell how a tumour had spread, and that therefore he could allocate a tumour to the pyloric group even though most of the body was involved. Shrinkage of the muscle after removal of the stomach could, he thought, produce distortion and so increase the difficulty of localization of the tumour.

Because of the spreading nature of cancer, a tumour beginning in the lower part of the body might well spread into the pyloric region, and at operation be considered as pyloric in origin. The converse is also true. Thus figures for the site of a gastric carcinoma may not be accurate, and therefore the ABO blood-group incidence at each site may not be accurate.

The work of Glynn *et al.* (1957) in investigating secretor substance in stomachs does not lend support to the supposition that there is an association between a particular blood group and a particular site. Secretor substance was found by them in both body and pyloric superficial zones in secretors, and was absent in non-secretors. In non-secretors the secretor substance was present in the deeper zones of both sites, and was replaced in non-secretors in the superficial zones of both by Le^a substance. Thus, so far as the A substance is concerned, their work shows that the body and pyloric regions do not differ, and one would therefore expect no difference in the blood groups of gastric cancer in the two sites. This investigation of the relationship between site and blood group is thus confirmed by the work of Glynn *et al.*

Sites of Gastric Ulcer

Billington (1956a) reported that there was a statistically significant association between group A and pyloric gastric ulcers, and between O and body gastric ulcers. Balme and Jennings (1957) confirmed the excess of group A in pyloric ulcers. In this series of ulcers there are more group O than group A in both pyloric and body ulcers. Comparison of the ulcers at these two sites shows, however, no statistical significance between the groups. Table XII shows the figures of these other two series and mine.

TABLE XII.—*Sites of Gastric Ulcers*

Series	Pyloric		Non-pyloric	
	O	A	O	A
Billington (1956a)	22	52	94	47
Balme and Jennings (1957)	20	29	76	67
Present series	76	37	281	204
Total	118	118	451	318

In view of the difference between these two series and the present one, it would not be reasonable to make a statistical overall comparison of site and blood group.

Histologically, there are some resemblances between pyloric glands and Brunner's glands in the duodenum, and sometimes Brunner's glands extend into the pyloric region for several centimetres (Maximov and Bloom, 1948). Greep (1954) states that Brunner's glands contain a dipeptidase similar to that found in pyloric and cardiac glands. He also quoted Plenk (1932), who thought that the cells in the cardiac glands of the oesophagus and in Brunner's glands in the duodenum are similar. Therefore it would be expected that there would be a similar ABO distribution in pyloric and duodenal ulcers. Clarke *et al.* (1955), in a mainly juxtapyloric group, found 77 ulcers of group O and 55 of group A. Sørensen (1957) also observed an excess of group O in juxtapyloric ulcers in which he included both gastric and duodenal ulcers diagnosed at operation. His figures were 278 of group O and 189 of group A. I collected, mainly from Monmouthshire hospitals, 417 cases of duodenal ulcers which had been seen at operation or at necropsy. Table XIII gives their ABO blood groups. Comparison between the O and A groups of the pyloric and duodenal ulcers shows no statistical significance ($\chi^2=0.77$; $P=0.38$), and the distribution of groups is of the same order as that in my cases of pyloric gastric ulcers. It is difficult, therefore, to reconcile the results of this series with those of

TABLE XIII.—*Blood Groups of Patients With Duodenal Ulcer Diagnosed at Operation or Necropsy*

O	A	B	AB	Total
228 (56·02%)	139 (34·15%)	33 (8·11%)	7 (1·72%)	407

Billington (1956a) and Balme and Jennings (1957), and until further series are published there can be no explanation of these divergences.

Summary

In Monmouthshire and Eastern Glamorganshire there was a statistically significant excess of group A in 746 cases of gastric cancer.

There was no statistical difference between 610 histologically proved gastric cancers and 170 diagnosed macroscopically.

In a series of 753 gastric cancers where the site in the stomach was known there was no association between the blood groups and the site of the tumour.

In Monmouthshire and Eastern Glamorganshire there was a statistically significant excess of group O in 975 cases of gastric ulcer.

No statistical differences were found in the ABO blood-group distribution between 690 cases of histologically proved chronic gastric ulcers and 316 macroscopically diagnosed gastric ulcers.

In a series of 661 histologically proved chronic gastric ulcers where the site was mentioned there was no evidence of an association between the blood groups and the site of the ulcer.

I am most grateful to many physicians and surgeons in hospitals in Monmouthshire and Glamorganshire and to the hospital records officers for much valuable assistance. I thank Dr. A. C. Kopec, of the Nuffield Blood Group Centre, for giving me the control figures for Glamorganshire and Monmouthshire, and particularly Dr. G. S. Andrews for advice on the preparation of this paper.

REFERENCES

Aird, I., Bentall, H. H., Mehigan, J. A., and Roberts, J. A. F. (1954). *Brit. med. J.*, **2**, 315.
—— —— and Roberts, J. A. F. (1953). Ibid., **1**, 799.
Alexander, W. (1921). *Brit. J. exp. Path.*, **2**, 66.
Balme, R. H. (1956). *Lancet*, **2**, 252.
—— and Jennings, D. (1957). Ibid., **1**, 1219.
Barber, M., and Dunsford, I. (1959). *Brit. med. J.*, **1**, 607.
Billington, B. P. (1956a). *Aust. Ann. Med.*, **5**, 141.
—— (1956b). *Lancet*, **2**, 859.
Brown, D. A. P., Melrose, A. G., and Wallace, J. (1956). *Brit. med. J.*, **2**, 135
Buchanan, J. A., and Higley, E. T. (1921). *Brit. J. exp. Path.*, **2**, 247.
Buckwalter, J. A., Wohlwend, E. B., Colter, D. C., Tidrick, R. T., and Knowler, L. A. (1956a). *J. Amer. med. Ass.*, **162**, 1210.
—— —— —— —— —— (1956b). Ibid., **162**, 1215.
—— —— —— —— —— (1957). *Surg. Gynec. Obstet.*, **104**, 176.
Cameron, J. M. (1958). *Lancet*, **1**, 239.
Clarke, C. A. (1955). *Proc. roy. Soc. Med.*, **48**, 291.
—— Cowan, W. K., Edwards, J. W., Howel-Evans, A. W., McConnell, R. B., Woodrow, J. C., and Sheppard, P. M. (1955). *Brit. med. J.*, **2**, 643.
—— Evans, D. A. P., McConnell, R. B., and Sheppard, P. M. (1959). Ibid., **1**, 603.
Einaudi, M. (1927). Quoted by Goldfeder and Fershing (1937).
Glynn, L. E., Holborow, E. J., and Johnson, G. D. (1957). *Lancet*, **2**, 1083.
Goldfeder, A., and Fershing, J. L. (1937). *Amer. J. Cancer*, **29**, 307.
Gorer, P. A. (1938). *Ann. Eugen. (Lond.)*, **8**, 219.
Greep, R. O. (1954). *Histology*. Blakiston, Philadelphia.
Haddock, D. R., and McConnell, R. B. (1956). *Lancet*, **2**, 146.
Heistø, H. (1956). *T. norske Lægeforen.*, **76**, 10. Quoted by Roberts (1957).
Hirschfeld, H., and Hittmair, A. (1926). Quoted by Goldfeder and Fershing (1937).
Hoche, O., and Moritsch, P. (1926). Quoted by Goldfeder and Fershing (1937).
Jennings, D., Balme, R. H., and Richardson, J. E. (1956). *Lancet*, **2**, 11.
Johannsen, E. W. (1925). *C.R. Soc. Biol. (Paris)*, **92**, 112.
Jordal, K. (1956). *Acta Med. leg. soc.*, **9**, Special No., p. 195.
Køster, K. H., Sindrup, E., and Seele, V. (1955). *Lancet*, **2**, 52.
Lessa, A., and Alarcao, J. (1949). Quoted by Roberts (1957).
McConnell, R. B., and Sheppard, P. M. (1957). *Acta genet. (Basel)*, **6**, 574.
Macklin, M. T. (1955). *Gastroenterology*, **29**, 507.
Macleod, K. I. E. (1937). *Brit. med. J.*, **2**, 745.
Matousek, M. (1935). Quoted by Goldfeder and Fershing (1937).
Maximov, A. A., and Bloom, W. (1948). *A Textbook of Histology*, 5th ed. Saunders, London.
Mayo, C. W., and Ferguson, J. O. (1953). *A.M.A. Arch. Surg.*, **66**, 406.
Mayr, E., Diamond, L. K., Levine, R. P., and Mayr, M. (1956). *Science*, **124**, 932.
Mitra, P. N. (1933). *Indian J. med. Res.*, **20**, 995.
Mosbech, J., and Hauze, M. (1956). First International Congress of Human Genetics, Copenhagen.
Plenk, H. (1932). Quoted by Greep (1954).
Roberts, J. A. F. (1953). *Heredity*, **7**, 361.
—— (1957). *Brit. J. prev. soc. Med.*, **11**, 107.
Segi, M., Fujisaku, S., Kurihara, M., and Moniwa, H. (1957). *Tôkohu J. exp. Med.*, **66**, 42.
Sheppard, P. M. (1953). *Brit. med. J.*, **1**, 1220.
Sørensen, K. H. (1957). *Dan. med. Bull.*, **4**, 45.
Speiser, P. (1956). *Krebsarzt*, **11**, 344.
Stocks, P. (1950). *Brit. J. Cancer*, **4**, 147.
Thomsen, O. (1931). Quoted by Goldfeder and Fershing (1937).
Tinney, W. S., and Watkins, C. H. (1941). *Proc. Mayo Clin.*, **16**, 613.
Ugelli, L. (1936). Quoted by Roberts (1957).
Videbaek, A., and Mosbech, J. (1954). *Acta med. scand.*, **149**, 137.
Wallace, J. (1954). *Brit. med. J.*, **2**, 534.
Walther, W. S., Raeburn, C., and Case, J. (1956). *Lancet*, **2**, 970.
Weiser, F. (1957). *Wien. med. Wschr.*, **107**, 737.
Woolf, C. M. (1955). *Univ. Calif. Publ. publ. Hlth*, **2**, 265.

DISTRIBUTION OF THE ABO BLOOD GROUPS IN CASES OF ACQUIRED HAEMOLYTIC ANAEMIA

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The association of various diseases with a particular blood group has been shown by several investigators. Aird, Bentall, and Roberts (1953) showed that carcinoma of the stomach was more prevalent among people of group A. Struthers (1951) found a deficiency of group O among young infants dying of bronchopneumonia in Glasgow. It was later shown that the incidence of gastric ulcers was higher among group O people (Aird, Bentall, Mehigan, and Roberts, 1954). Other associations have been reported and reviewed (Roberts, 1957).

Hunt and Lucia (1953) noted that out of a series of 27 haemolytic anaemia patients 21 were of group O. This corresponded with an incidence of 77.8% among group O, while the control series of the general population for which the subjects were drawn showed an incidence of 45% group O. Dacie (1954) found no significant difference in the blood-group distribution of his series of 28 cases. Clemens and Walsh (1955) investigated a series of 66 cases and found that the frequency of the gene O is 0.7977 among the patients with haemolytic anaemia, but only 0.6933 among the control series. There is an excess of group O which is significant at the 5% level, but not so marked as in the series of Hunt and Lucia (1953).

The present series consists of 127 patients, in each of whom a positive anti-human-globulin test was obtained,

together with clinical and haematological evidence for the diagnosis of acquired haemolytic anaemia.

The distribution was as follows:

	Controls (6,000)	Acquired Haemolytic Anaemias (127)
O	45.39%	47.24% (60 cases)
A	43.28%	40.16% (51 „)
AB	2.748%	5.51% (7 „)
B	8.582%	7.09% (9 „)

The Rh distribution was:

	Acquired Haemolytic Anaemias	Controls (6,000)
Rh +ve (D +ve)	82.10%	82.16%
Rh −ve (D −ve)	17.90%	17.84%

From these figures there is no reason to suppose there is a strong association between blood group O and the disease, or that there is any marked abnormality.

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REFERENCES

Aird, I., Bentnall, H. H. R., Mehigan, J. A., and Roberts, J. A. F. (1954). *Brit. med. J.*, **2**, 315.
—— —— and Roberts, J. A. F. (1953). Ibid., **1**, 799.
Clemens, K., and Walsh, R. J. (1955). *Aust. J. Sci.*, **17**, 136.
Dacie, J. V. (1954). *The Haemolytic Anaemias. Congenital and Acquired*. Churchill, London.
Hunt, M. L., and Lucia, S. P. (1953). *Science*, **118**, 183.
Roberts, J. A. F. (1957). *Brit. J. prev. soc. Med.*, **11**, 3.
Struthers, D. (1951). Ibid., **5**, 223.

HYPERTENSIVE DISEASE IN JAMAICAN NECROPSY MATERIAL

BY

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In an investigation of the adrenal glands in hypertension it was noticed that hypertensive disease seemed to be common in necropsy material here in Jamaica. Therefore the incidence and type of hypertensive disease in adult Jamaicans coming to necropsy were investigated.

Methods and Materials

The clinical notes and necropsy data of 694 adult Jamaicans of mixed racial descent were examined. No selection of cases, which for practical purposes were consecutive, was made except that 13 were discarded because there was doubt whether they were normotensive or hypertensive.

The remaining 681 cases were grouped according to whether they were normotensive or hypertensive. Criteria used were the clinical history, blood-pressure, heart weight, thickness of left ventricle, weight of kidneys, and vascular changes in the arterioles. Repeated diastolic readings of 100 mm. Hg or over were accepted as evidence of hypertension. A few known hypertensives in terminal cardiac failure had lower readings. Cases of sudden death with no history were regarded as hypertensive if they showed an increase in heart weight (above 400 g. in the male and 350 g. in the female) due to left ventricular hypertrophy (in the absence of a valvular lesion), as well as vascular lesions of hypertension. The hypertensive cases were divided into essential and renal groups.

Results

Hypertensive disease was found in 211 (31%) out of 681 necropsies (see Table): 132 (62%) were judged to be essential, and in 79 (38%) renal disease was present. The renal lesions were: pylonephritis in 46 cases, glomerulonephritis in 20, and diabetic glomerulosclerosis in 3. The remaining 10 included amyloid disease, renal hypoplasia, carcinoma, and narrowing of a renal artery.

Incidence of Hypertension in 681 *Necropsies*

Age	No. of Necropsies		No. with Hypertension	
	Male	Female	Male	Female
16–19	10	15	3	1
20–29	45	46	7	6
30–39	56	50	17	11
40–49	78	70	22	22
50–59	93	44	37	14
60–69	63	42	25	14
70–79	33	23	15	12
80 and over	6	7	2	3
Total ..	384	297	128	83

In order to assess the relationship of pyelonephritis to hypertension in more detail, a study was made of a series of 250 consecutive adult necropsies which I had performed or witnessed. There were 40 cases of pyelonephritis (16%). In 11 it was associated with some obstruction in the urinary tract, and in seven with diabetes mellitus. Of the 40 cases with pyelonephritis, 26 had hypertension, but in 5 of these the pyelonephritis was mild, and associated with some other severe renal disease. In four others the pyelonephritis was thought to be too mild to account for the hypertension. Of the 17 cases of hypertension in which pylonephritis was thought to be the essential lesion the disease was chronic. In 14 of these it was still active.

Hypertension was concerned in the death of 139 of the 211 cases of hypertension in the larger series: 40 died in cardiac failure, 38 in renal failure, 17 in cardiac and renal failure, 26 with cerebral haemorrhage, and 18 from other related causes, including cerebral softenings and hypertensive encephalopathy.

Discussion

There is evidence that hypertension is more common in the African than in the Caucasian. Reviewing the extensive literature on the subject, Bays and Scrimshaw (1953) concluded that racial differences in the incidence of hypertension exist and that the incidence is higher in the African and American negro than in the Caucasian. The majority of Jamaicans are of African or mixed African and Caucasian descent, but little is known about the incidence of hypertension and hypertensive disease here in Jamaica. Kean (1941) investigated racial differences in the incidence of hypertension in Panama and found hypertension was seven times more common in the West Indian immigrant than in the Panamanian. From a study of necropsy material Taylor (1945) concluded that hypertensive disease was six times more common in West Indian immigrants than in Panamanians, and three times more common than in Caucasians resident in Panama. He also found pylonephritis was more frequent in the West Indian group than in other groups.

In my Jamaican necropsy material 30.9% showed evidence of hypertension. This comes close to Taylor's figure of 32.7% for West Indian immigrants, and is to be compared with the 10.4% he quotes for Caucasians

resident in Panama, and the 5.2% for Panamanians. The number of Caucasians coming to necropsy at University College Hospital, Jamaica, was small, but, of the 18 cases so described and sufficiently documented, only one had hypertensive disease. These comparisons are of interest, but no conclusion regarding the incidence of hypertension in the general population can be drawn from them. The findings show, however, that the ratio of renal (38%) to essential hypertension (62%) is high, since it is generally accepted that in 90% of hypertensives there is no kidney disease to explain the elevation of blood-pressure. Though the presence of renal disease in some cases of hypertension may be coincidental and in others the severity of the renal disease may have been misjudged and the cases wrongly designated renal hypertension, it is unlikely that these factors would alter the ratio to any great extent.

The commonest renal lesion was pyelonephritis, and in the smaller series of 250 cases previously mentioned 40 (16%) had pyelonephritis. This approaches Taylor's figure of 19.6% for West Indian immigrants into Panama, and is to be compared with the 8.2% he quotes for Caucasians resident in Panama. The reasons for this apparently high incidence of pyelonephritis are not known. The reasons for this apparently high incidence of pyelonephritis are not known. A number of factors, including urinary obstruction, diabetes mellitus, and venereal disease, may be concerned. Of the 40 cases of pyelonephritis 11 were associated with obstruction and 7 with diabetes mellitus. The incidence of venereal disease in the present series is not known, but it is probably higher than would be encountered in present-day European material.

In the same series of 250 cases there were no fewer than 11 cases of diffuse glomerulonephritis (4.4%). This suggests that climate plays no important part in the aetiology of the condition, and that infections with the group A beta-haemolytic streptococcus may be common here.

Raaschou (1949) showed that a normal or near-normal liver function was needed if hypertension was to be maintained. Loyke (1955) demonstrated that hypertension did not usually occur in the presence of cirrhosis provided the kidneys were normal, and also that established hypertension was reversed to normal pressure with the onset of cirrhosis. In my material 2 out of 26 cases of cirrhosis had normal blood-pressure readings but gave a history of hypertension or had anatomical evidence of hypertension.

Summary

Evidence of hypertension was found in 31% of adult Jamaicans coming to necropsy, but no conclusion regarding the incidence of hypertension in the general population can be drawn from this finding.

The ratio of presumed renal (38%) to essential hypertension (62%) was high. Pyelonephritis was the commonest lesion.

Hypertension was concerned in the death of 20% of Jamaicans coming to necropsy.

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REFERENCES

Bays, R. P., and Scrimshaw, N. S. (1953). *Circulation*, **8**, 655.
Kean, B. H. (1941). *Arch. intern. Med.*, **68**, 466.
Loyke, H. F. (1955). *Amer. J. med. Sci.*, **230**, 627.
Raaschou, F. (1949). *Nord. Med.*, **42**, 1791.
Taylor, C. E. (1945). *Amer. J. Path.*, **21**, 1031.

TWO CASES OF LOCKED TWINS

BY

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This very rare condition is believed to occur once in every 90,000 deliveries or once in every 1,000 twin deliveries. It is thus felt justifiable to report these two cases.

Case 1

An unbooked primigravida aged 26 was admitted on October 22, 1958, to the Obstetric department at Queen's Park Hospital, Blackburn, as a case of twin pregnancy with ruptured membranes. There were no contractions. The pregnancy had advanced to just over 36 weeks.

The antenatal history showed that an external cephalic version had been performed at the 31st week. The breech presentation recurred, and version was repeated two weeks later. Twin pregnancy had then been suspected, and an *x*-ray examination confirmed the presence of twins. The leading foetus was reported to be presenting by the breech with its spine to the left, yet it was difficult to decide whether the legs were flexed or extended. The second twin was presenting by the vertex, and its spine was to the right.

The membranes had ruptured 11 hours before admission, but the patient stated that the amount of liquor that had drained was not excessive. She felt no uterine contractions. The uterus was enlarged to the level of the ensiform cartilage. The pregnancy seemed to have been progressing satisfactorily. The blood-pressure was 125/80. The haemoglobin was 73% (10.9 g./100 ml.). Urine examination was negative. Two foetal hearts were heard—one in the right iliac fossa and the other to the left of the umbilicus. A vaginal examination showed the cervix to be closed, and a vertex was thought to be presenting at the brim (this was probably the vertex of the second twin).

Complete bed rest, prophylactic penicillin, and oral iron therapy were prescribed.

Four days later labour began, but the contractions were rather irregular and infrequent. Next day the cervix was found to be three-quarters dilated and a flexed breech was presenting at the level of the brim. The contractions had ceased for approximately four hours. A "pitocin" drip containing 10 units per litre was started intravenously. The contractions became more frequent, but were short in duration. At 8.30 p.m. the cervix was found to be fully dilated on vaginal examination and the breech had reached the mid-cavity in the left sacro-transverse position. Two hours later the breech was just showing at the vulva and the contractions were quite strong. An anaesthetist was present, as it was customary to give the patient a light anaesthetic for the delivery of the aftercoming head. For another hour no advance was noticed, and it was decided to assist delivery.

An episiotomy was performed after infiltration of the perineum with 1% lignocaine. The legs were brought down and with gentle traction the baby was delivered to just above the umbilicus. The patient was then very apprehensive and uncooperative, and it was decided to proceed with the general anaesthetic at once and extract the baby. This was begun (thiopentone, nitrous oxide, oxygen, and ether), and further traction could achieve delivery to the middle of the scapulae but no further, in spite of bringing down the arms. Further vaginal examination revealed the head of the second twin to be engaged in the pelvis. It was then realized that the head felt above the symphysis pubis was that of the first twin. The head of

the second twin was then pushed up, this being assisted by pushing upwards and inwards on the axillae of the first twin. Unlocking was achieved after a little difficulty. The anaesthesia was, however, fairly deep. The first twin was then delivered easily, the head being delivered by the Mauriceau–Smellie–Veit manœuvre. It had rather a long neck and was deeply shocked.

Five minutes later the second amniotic sac ruptured spontaneously and the head engaged in the pelvis in the right occipito-posterior position. It was rotated and delivered by forceps 15 minutes after delivery of the first twin. Ergometrine, 0.5 mg., was given intravenously.

The placenta was binovular, being formed of two partially fused placentae. It weighed 2 lb. (907 g.). The episiotomy was repaired. The puerperium was uneventful.

The first twin was a female weighing 3 lb. 4 oz. (1,475 g.). Its crown–heel length was 16 in. (40.6 cm.) and its head circumference measured 10½ in. (26.7 cm.). It quickly recovered and gained weight steadily. Apart from an attack of staphylococcal enteritis on the sixth day its progress was normal. She was quite well, and weighed 10 lb. 10 oz. (4,820 g.) when 5 months old.

The second twin was a male weighing 4 lb. 14 oz. (2,210 g.). Its length was 18 in. (45.7 cm.) and its head circumference measured 12¼ in. (31 cm.). It made good progress, and when seen five months later weighed 13 lb. 11 oz. (6,210 g.).

Case 2

A primigravida aged 22 was admitted on April 20, 1959, to the obstetric department of the City Hospital, Derby. She was transferred from a near-by maternity home on account of premature rupture of membranes. The pregnancy had reached the 32nd week, and had apparently been quite uneventful.

The membranes ruptured eight hours before admission, but she had had no contractions. She was thinly built. The fundus uteri was two fingerbreadths below the ensiform cartilage. The uterus was rather tense, but two foetal heads could be palpated—one in the left hypochondrium and the other in the right iliac fossa. A provisional diagnosis of twin pregnancy was made. Her blood-pressure was 130/80 and examination of the urine was negative. Her haemoglobin was 75% Haldane (11.1 g./100 ml.). Bed rest was prescribed.

A vaginal examination disclosed a long cervix which admitted one finger. The presenting part was at the level of the brim and was thought to be a breech. *X*-ray examination confirmed the presence of twins. The leading foetus was presenting by the breech with its back to the left. The second twin presented by the vertex and its back was to the right.

For the next nine days liquor amnii continued to drain per vaginam. On April 29 labour started. The contractions were strong and frequent, and after two and a half hours vaginal examination revealed the cervix to be fully dilated. A complete breech occupied the lower pelvic strait and preparations were made for delivery.

A pudendal-block anaesthesia, using 1% lignocaine, was carried out followed by an episiotomy. The baby was then delivered spontaneously to the level of the inferior angles of the scapulae. The arms were easily brought down, but further delivery was impossible. The left hand was then introduced in the vagina and the head of the second twin was found engaged in the pelvis.

General anaesthesia was then quickly induced with nitrous oxide, oxygen, and ether, but disengagement could not be achieved until a deep level of anaesthesia had been reached. Pressure upwards on the head of the second twin and on the trunk of the first resulted in disengagement. The first twin was then extracted quite easily, using the Mauriceau–Smellie–Veit technique for the after-coming head, but was stillborn. Its heart-beat was noticed to have ceased a few minutes before completion of delivery. The time interval from the birth of the umbilicus to the completion of the delivery of the head was 17 minutes.

The second twin then engaged in the left occipito-posterior position. The membranes were ruptured artificially. Neville–Barnes forceps were applied after an unsuccessful attempt at manual rotation and the baby was delivered face to pubis, 10 minutes after delivery of the first twin. It cried immediately.

Two separate placentae were delivered, weighing 12 oz. (340 g.) and 10 oz. (283 g.) respectively.

The first twin was a female and weighed 4 lb. 3 oz. (1,900 g.). It measured (crown–heel) 18 in. (45.7 cm.). Its head circumference was 12¼ in. (31 cm.).

The second twin was also a female and weighed 4 lb. 2 oz. (1,870 g.). It measured 17¼ in. (43.8 cm.). It had an equal head circumference. It made good progress, and when seen at 11 weeks of age it weighed 8 lb. 14 oz. (4,025 g.) and was quite well.

Incidence

Jahkola (quoted by Falke, 1939) collected 83 cases of locked twins from the literature up to 1936. Lawrence (1949) collected 28 cases published from 1907 until 1946 and reported three cases. Nissen (1958) reviewed the literature from 1882 until April, 1957, and collected 69 cases, including one of his own. In an addendum he also referred to one case described by Colliton. I accidentally came across a case not included in Nissen's collection. This was published by McKenzie and Quist (1956), who described a chin-to-chin locking diagnosed radiologically and delivered by caesarean section. From April, 1957, up to the articles indexed in the May, 1959, issue of the Current List of Medical Literature only three published cases could be found. Kreis and Miller (1958) described a case of chin-to-chin locking. An attempt at disengagement failed, as did a trial of the Kimball and Rand (1950) technique of delivering the head of the second twin with Piper forceps past the first twin. Ultimately decapitation of the first twin had to be performed before delivering the second twin alive. The first twin weighed 3 lb. 15 oz. (1,786 g.) and the second 4 lb. 11 oz. (2,126 g.). Percival (1959) described two unpublished cases of Sir Eardley Holland's. In both cases the presentation was cephalic in either twin. One case was delivered vaginally after disengagement and the other by caesarean section.

von Braun (quoted by Brews, 1948) observed only one case of twin locking in 90,000 deliveries in Vienna, and this estimated incidence of the condition is quoted by most writers. Horder (1944) and Stenström (1951) believe the incidence to be higher than von Braun's estimation. It must be difficult to estimate the real incidence of locking, as not all cases are published. I know of one such case.

Discussion

Lawrence (1949) classified cases of locking into four groups according to the respective presentation of the twins. These are, in order of frequency, breech and vertex, vertex and vertex, vertex and transverse, and breech and breech. Nissen (1958) followed Lawrence's classification. In his collection a little more than two-thirds belonged to the first group.

The two reported cases also belonged to the first group, and locking occurred between chin and chin.

Both cases occurred in primigravidae; 72% of Nissen's collection were in primigravidae. This is believed to be aetiologically significant.

In both cases premature rupture of the membranes of the leading foetus occurred. It was not, however, noticed that the second amniotic sac contained an unusually small amount of liquor; a fact which many commentators think predisposes to the occurrence of locking. It is, however, reasonable to assume that a reduction of the amniotic fluid in either sac may favour locking of the twins as a result of closer approximation.

A third factor which is considered significant in the aetiology is a large-sized pelvis in relation to the sizes of the babies. In the two cases reported the babies were small, but the mothers were not of unduly big stature. In fact, the height of the mother in Case 2 was 5 ft. 1 in. (155 cm). I could not find a record of the height in the first case, but her pelvis was not of exceptionally large dimensions clinically.

Another factor thought to be contributory is hypertonicity of the uterus. This was so in the second case but not in the first. In fact, in the latter, the uterine tone was very low and she was completely inert at some stages of labour.

Stenström (1951) found a higher incidence in uniovular twins. The two cases reported were binovular.

The fact that the majority of the leading foetuses in cases of breech-and-vertex twin deliveries, where locking occurred between head and neck or chin and chin, presented as a complete breech is worth mentioning. This, so far as could be found, has not been commented upon by previous writers. It seems likely that a breach with flexed legs in the leading twin favours locking more so than in a breech with extended legs, which would prevent close contact between the head of the second twin and the thorax or neck of the first. A breech with flexed legs presented in the two cases reported.

Wright (1942) published three cases of locked twins. In two of them locking occurred between chin and chin, and in each case the first twin presented as a footling. In his third case locking occurred between the neck of the first twin, which again presented as a footling, and the flexed breech of the second twin. In the cases of Hunter (1927), Moore (1933), Spence (1937), Bowles (1938), Whitfield (1938), Nicolson (1942), Bradlow (1944), Greig (1946), Geggie (1947), Lawrence (1949, Case 3), Williamson (1953), and Swann (1957, Case 2), where locking occurred between chin and chin, the first twin presented as a flexed breech or a footling. Stenström (1951) described two cases of twin locking where the first twin presented as a flexed breech in one case in which decapitation had to be resorted to, and as a footling in the other where delivery was achieved by caesarean section. In the cases of Russell (1938), Love (1944), Macintyre and Barr (1951) (2 cases), and Gordon (1956) no specific mention was made of whether the legs were flexed or extended, but the description was often suggestive of a flexed breech. Lattuada (1951) described a case where locking occurred between the neck and chest of the first twin, which presented by the breech, and the head of the second twin, presenting as a vertex. The diagnosis was made radiologically, and consequently the delivery was accomplished by caesarean section. There was no mention of the type of breech presenting, but from the *x*-ray film published it appeared quite likely that the legs were flexed.

In only two cases was it mentioned that the breech was a frank one (Kreis and Millet, 1958; Kimball and Rand, 1950).

Thus out of 27 cases reviewed (including the two cases here reported), where the first twin presented by the breech, 20 first twins had flexed legs or presented as a footling, in 5 cases the description was suggestive, and in 2 the breech was a frank one.

Treatment

Treatment can hardly be premeditated. Locking is usually diagnosed only during the delivery and very seldom during labour. Each case has to be managed individually. Disengagement should be attempted first, preferably under deep anaesthesia. Anaesthesia had already been administered before the diagnosis was made in Case 1, and thus no time was wasted in its induction as was done in the second case. If disengagement fails, decapitation of the first twin becomes essential, though caesarean section could be carried out, particularly if it is felt that decapitation would be associated with a greater risk of maternal trauma. Wright (1942) quotes McClintock, in Smellie's *Treatise of Midwifery*, who cited one case of locked twins in which decapitation was performed "with a bass string wrapped round with wire of a pianoforte."

Caesarean section has a place in cases of locking or "collision" between head and head or breech and breech when disengagement is not possible vaginally (Dawson, 1936; Preston, 1937), especially if the amount of liquor left is small (Cunningham, 1947).

Kimball and Rand (1950) described a case of chin-to-chin locking where the second twin was delivered with forceps past the first twin, which had been delivered up to the shoulders. The first twin weighed 4 lb. (1,814 g.) and the second 4 lb. 12 oz. (2,154 g.). Both were delivered alive. No mention was made of the size of the pelvis, but it must have been a large one.

Summary

Two cases of locked twins, chin to chin, are described. Disengagement vaginally was possible in both cases. In the second case the first twin was lost. The first twin was saved in the first case, where the mother was already under an anaesthetic. The fact that in the great majority of published cases of chin-to-chin locking the leading twin presented as a flexed breech is emphasized and is thought to bear an aetiological relationship.

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REFERENCES

Bowles, H. E. (1938). *J. Amer. med. Ass.*, **110**, 1551.
Bradlow, B. A. (1944). *Brit. med. J.*, **2**, 532.
Brews, A. (1948). Eden and Holland's *Manual of Obstetrics*, 9th ed., p. 396. Churchill, London.
Cunningham, W. D. (1947). *Med. J. Aust.*, **1**, 494.
Dawson, J. B. (1936). *J. Obstet. Gynaec. Brit. Emp.*, **43**, 507.
Falke, L. A. (1939). *Zbl. Gynäk.*, **63**, 66.
Geggie, J. H. S. (1947). *Canad. med. Ass. J.*, **57**, 381.
Gordon, R. (1956). *S. Afr. med. J.*, **30**, 661.
Greig, D. S. (1946). *Brit. med. J.*, **1**, 13.
Horder, C. A. (1944). Ibid., **1**, 783.

Hunter, J. W. A. (1927). *N. Engl. Obstet. Gynaec. Soc. Trans.*, p. 45.
Kimball, A. P., and Rand, P. R. (1950). *Amer. J. Obstet. Gynec.*, **59**, 1167.
Kreis, D. J., and Miller, R. T. (1958). Ibid., **76**, 1334.
Lattuada, H. P. (1951). *Amer. J. Surg.*, **81**, 448.
Lawrence, R. F. (1949). *J. Obstet. Gynaec. Brit. Emp.*, **56**, 58.
Love, M. (1944). *Brit. med. J.*, **2**, 12.
Macintyre, I. D., and Barr, G. M. (1951). Ibid., **1**, 1123.
McKenzie, C. H., and Quist, H. W., jun. (1956). *Minn. Med.*, **39**, 35.
Moore, J. (1933). *Brit. med. J.*, **2**, 56.
Nicolson, E. L. (1942). *J. Obstet. Gynaec. Brit. Emp.*, **49**, 162.
Nissen, E. D. (1958). *Obstet. and Gynaec.*, **11**, 514.
Percival, R. (1959). In *British Obstetric and Gynaecological Practice* (*Obstetrics* volume edited by Sir Eardley Holland), 2nd ed., p. 685. Heinemann, London.
Preston, P. G. (1937). *J. Obstet. Gynaec. Brit. Emp.*, **44**, 723.
Russell, J. J. (1938). *Brit. med. J.*, **2**, 1205.
Spence, J. H. (1937). Ibid., **2**, 1222.
Stenström, B. (1951). *Acta obstet. Gynec. scand.*, **31**, 1.
Swann, R. O. (1957). *Amer. J. Obstet. Gynec.*, **73**, 907.
Whitfield, C. A. (1937). *J. roy. Army med. Cps*, **69**, 401.
Williamson, M. (1953). *J. Obstet. Gynaec. Brit. Emp.*, **60**, 421.
Wright, S. W. (1942). *Lancet*, **2**, 212.

IS TRICHOMONAL INFESTATION A VENEREAL DISEASE?

BY

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The evidence that *Trichomonas vaginalis* infestations are transmitted by sexual intercourse in most cases has been reviewed by Trussell (1947). He argued that the organism has its commonest habitat in the vagina, which suggests that it may be implanted by coitus. Many cases have been reported in which both sexual partners have been infected and in which the onset of symptoms in one of them dated from coitus with the other. The age when infestations occurred most commonly was suggestive of a venereal transmission. The condition was uncommon among children and virgins but most common between the ages of 16 and 35 years, which is usually the period of greatest sexual activity. Trussell pointed out that the disease is twice as common in negro women as in whites in the United States of America, and, though this has been attributed to poor hygienic habits, it could equally well be explained by greater sexual promiscuity. The frequent association of gonococci and trichomonads in the same patient suggested sexual intercourse as a means of transmission. King, Mascall, and Price (1936) were the first to point out the frequent association of the two diseases. Greenblatt (1945) found 66% of 127 prostitutes examined to have *T. vaginalis*, and 62.5% of another group of women with gonorrhoea to be also infected wih the parasite. King and Gallagher (1946) found *T. vaginalis* in 30 out of 81 female patients with gonorrhoea.

Trussell also pointed out that the increased incidence of infestation in pregnant women suggested that infection might be favoured by the unprotected sexual act. Some authors have suggested that the routine use of chemical contraceptives gave some protection against infection. Stein (1943) believed that trichomonal and mycotic infections were rare among women who used acid jellies for contraception. Wessels (1943), after investigating the records of 1,471 patients who practised contraception, was impressed by the low incidence of vaginitis.

At the First International Symposium on Trichomonal Infestations, held at Rheims in May, 1957, it was agreed by the majority of the delegates that human trichomoniasis was usually transmitted by sexual intercourse, that it was widespread throughout the world, and that the frequency of the condition was probably increasing.

However, the possibility of transmission of the parasite by other means has been suggested by several authors and cannot always be excluded. Instances have been reported of infection in members of the same family—for example, the mother and the female infants. Brady and Reid (1942) observed vaginal infection in a woman and in her 5-weeks-old baby. Trussell, Wilson, Longwell, and Laughlin (1942) examined 41 babies of women infected with *T. vaginalis*, and found that two were infected. They suggested that female babies may become infected from their mothers during birth.

McCullagh (1953) thought that infection was often transmitted by contaminated lavatory seats, but he gave no evidence to support this view. Whittington (1957) carried out experiments on the possibility of infection being transmitted in this way. She showed that *T. vaginalis* can survive for some time on lavatory seats, and is sometimes deposited on the seat by infected patients. The possibility of accidental infection by this means may therefore exist in some cases.

Lanceley and McEntegart (1953) regarded trichomoniasis as a venereal disease in the majority of cases, but believed that there was evidence to suggest that some infections were accidental, and warned against careless technique in vaginal examinations because they believed that infection could be spread by this means.

Other possible sources of infection that have been suggested include douche nozzles, enema syringes, towels, underwear, internal sanitary towels, and surgical instruments. Transmission by these means has never been proved.

Some investigators have regarded the intestine as the source of infection, believing that intestinal trichomonads could become adapted to the vagina. There is, however, no evidence that they can be successfully established in the human vagina (Stabler, Feo, and Rakoff, 1940). Nor is there any positive evidence to suggest that oral trichomonads will produce vaginal disease. The majority opinion at the Rheims Symposium rejected the view that contamination occurred from alimentary or animal origins.

Finally, it has been suggested that infection might be acquired by drinking infected water or eating infected food, or that it can be transmitted in swimming-pools or swimming-baths by infected water. Little or no positive evidence has been produced to support these views, and the balance of probability seems to be against such methods of transmission.

To summarize, therefore, the published evidence suggests that the most frequent method of transmission of *T. vaginalis* is by the sexual act, though in a small proportion of cases infection may be acquired by other means.

Present Investigation

The object of this communication is to present further evidence in support of the belief that *T. vaginalis* infections are usually venereally transmitted.

The patients all attended the departments for venereal diseases at three large London teaching hospitals—the London Hospital, St. Thomas's Hospital, and St. Bartholomew's Hospital. Each patient was thoroughly examined for evidence of genital infection by clinical and bacteriological methods and for evidence of other disease by physical examination. *T. vaginalis* was looked for in wet smears of the urethral or vaginal secretions, using the 1/12-in. (2-mm.) objective of the microscope with either normal or dark-ground illumination. Cultures, using the medium described by Feinberg and Whittington (1957) were also performed in most cases. In a small number of cases the centrifuged deposit of urine was also examined microscopically for trichomonads.

Results

This is an analysis of 56 male patients with *T. vaginalis* urethritis, whose female sexual contacts were available for examination, making a total of 112 subjects. The male patients in the series were selected in the sense that they were seen first and diagnosed as having a urethritis caused by *T. vaginalis*. Their female sexual partners were then requested to attend for examination, and were all found to have *T. vaginalis* vaginitis. Thus, *T. vaginalis* was demonstrated in both partners in 56 couples, who admitted to sexual intercourse together.

Thirty of the couples attended the London Hospital, 23 couples St. Thomas's Hospital, and 3 St. Bartholomew's Hospital.

The average age of the men was 33 years and of the women 24 years. Thirty of the women stated that they were the wives of their sexual partners, and 24 said that they were friends. In two cases the liaison was described as casual, and intercourse was said to have occurred on one occasion only.

Only two of the couples stated that they regularly used chemical contraceptives, and in both cases these were used in association with an occlusive diaphragm. Six couples claimed that they always used a condom, and that intercourse had not taken place without it. The remaining 48 couples either took no precautions at all or used various methods of contraception on isolated occasions only.

Five of the women stated that they were virgins until they had intercourse with their present partners. All five of the men concerned admitted to previous sexual experience. The five women all stated that they had symptoms from their infestation, and that these came on from 5 to 28 days after their first intercourse.

In six of the couples gonococcal urethritis or cervicitis was found to be present in addition to the infestation with *T. vaginalis*. Five men were subsequently found to have strictures of the urethra when urethroscopy was performed as part of the tests of cure. All the five were attending the London Hospital, and it is interesting and instructive that it was only at that hospital that urethroscopy formed part of the routine tests of cure.

The men were given posterior irrigations with either a 1 in 8,000 solution of oxycyanide of mercury or potassium permanganate or a 1 in 10,000 solution of dequalinium chloride ("dequadin"). The women were treated with acetarsol vaginal pessaries, using two pessaries each night for 14 successive nights. Abstinence from sexual intercourse was advised in all cases. No attempt has been made to assess the results of treatment owing to the high defaulter rate and the inadequate period of follow-up in many of the couples.

Discussion

Many authors have, in the past, considered trichomonal vaginitis as a venereal disease (Trussell, 1947; Bauer, 1957; Chappaz, 1957; Durel and Roiron, 1957; Keutel, 1957). Many, but by no means all, make a practice of investigating the sexual partners of patients infected with *T. vaginalis*. One of the reasons for neglecting to do so may be the difficulty, at a single examination, of demonstrating the parasite in male patients who are contacts of women with *T. vaginalis*. However, with improved diagnostic facilities and techniques it is being found more often in men.

The parasite is undoubtedly one of the causes of non-gonococcal urethritis, but it may be present in the male urethra without causing symptoms or signs, or a mild urethral discharge may be overlooked by the patient. Whittington (1957) and Nicol (1958) have demonstrated that the routine use of cultural methods, employing the Feinberg–Whittington medium, increased the number of cases of trichomonal urethritis diagnosed in a venereal disease clinic, and recommended this method as a routine aid to diagnosis. The examination of an early morning "scrape" from the urethral wall and the investigation of the centrifuged deposit of urine are also likely to increase the number of positive cases.

From the evidence presented here it seems reasonable to conclude that *T. vaginalis* infestations are venereally transmitted in most cases. It is probable that infection sometimes arises from other sources, just as authentic cases of syphilis and gonorrhoea acquired in a non-venereal manner are well known. If it is accepted that the condition is a venereal disease, the sexual partners of all patients with *T. vaginalis* infections should be examined, and, if necessary, treated. Sexual intercourse should not take place until the parasite has been eradicated from the genital tract of both partners. These measures may lead to some improvement in the unsatisfactory results at present obtained with the various forms of treatment.

Summary and Conclusions

Trichomonas vaginalis was demonstrated in the female sexual partners of 56 males with *T. vaginalis* urethritis.

The evidence that *T. vaginalis* causes venereal infection is reviewed, and it is suggested that the evidence presented further supports this theory.

Patients with *T. vaginalis* infections should be referred to venereal disease clinics so that the necessary history of sexual contacts can be obtained. These contacts can then be traced, examined, and treated if they are found to be infected with *T. vaginalis*.

Sexual intercourse should be forbidden until *T. vaginalis* is eradicated from the genital tracts of both partners.

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REFERENCES

Bauer, H. (1957). In *Les Infestations à Trichomonas*, p. 21. Masson, Paris.
Brady, L., and Reid, R. D. (1942). *Ann. Surg.*, **115**, 840.
Chappaz, G. (1957). In *Les Infestations à Trichomonas*, p. 161. Masson, Paris.
Durel, P., and Roiron, V. (1957). Ibid., p. 114.
Feinberg, J. G., and Whittington, M. J. (1957). *J. clin. Path.*, **10**, 327.
Greenblatt, R. B. (1945). *West J. Surg.*, **53**, 135.
Keutel, H. J. (1957). In *Les Infestations à Trichomonas*, p. 151. Masson, Paris.
King, A. J., and Gallagher, E. (1946). *Lancet*, **1**, 916.
—— Mascal, W. N., and Price, I. N. O. (1936). Ibid., **2**, 18.
Lanceley, F., and McEntegart, M. G. (1953). Ibid., **1**, 668.
McCullagh, W. M. H. (1953). Ibid., **1**, 698.
Nicol, C. S. (1958). *Brit. J. vener. Dis.*, **34**, 192.
Stabler, R. M., Feo, L. G., and Rakoff, A. E. (1940). *J. Parasit.*, **26**, Suppl. p. 22.
Stein, I. (19 3). Quoted by R. E. Trussell, *Trichomonas Vaginalis and Trichomoniasis*, 1947, p. 107. Blackwell, Oxford.
Trussell, R. E. (1947). Ibid., p. 103. Blackwell, Oxford.
—— Wilson, M. E., Longwell, F. H., and Laughlin, K. A. (1942). *Amer. J. Obstet. Gynec.*, **44**, 292.
Wessels, M. (1943). Quoted by R. E. Trussell, *Trichomonas Vaginalis and Trichomoniasis*, p. 107. Blackwell, Oxford.
Whittington, M. J. (1957). *Brit. J. vener. Dis.*, **33**, 80.

RECOGNITION OF EMOTIONAL DISTURBANCE AND THE PREVENTION OF SUICIDE

BY

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More than 5,000 persons die annually by their own hand in England and Wales, and there is reason to suppose that their number will increase as the age structure of the population changes (Swinscow, 1951). There is no doubt about the size of the problem of suicide or of its claims for attention.

Sainsbury (1955) examined the social factors which favour suicide and suggested fields of study which might lead to the prevention of suicide through a programme of mental hygiene, but can any substantial proportion of the present toll of suicides be prevented now by medical action? The answer must depend upon how many potential suicides show signs which are recognizable as danger signals calling for medical help, how many of these danger signals are recognized as such, and how many would-be suicides, if recognized as emotionally ill, are then responsive to psychiatric treatment.

With these questions in mind the coroners' records of the suicides which occurred throughout Wales in the five years 1951–5 were examined. During the five years 881 suicides occurred among the permanent residents of the 12 Welsh counties (excluding Monmouthshire). Objection can be made to the validity of some kinds of information obtained from these sources. Witnesses may have been unintelligent, uninformed, unobservant, or biased. Despite this difficulty, however, it is probable that evidence regarding the behaviour, the demeanour, and the medical treatment of the suicides was substantially true.

The information so obtained fell into two classes—the earlier medical condition within about the last year of the suicides' life, and the condition some hours or minutes before death.

The Earlier Condition

Of the 881 suicides, 689 (78.2%) were known to have been under a doctor's care during the months before they died, and many of these were treated for conditions which appeared to have probably been related to psychiatric illnesses. Hypochondriasis, headaches, depression, or merely "nerves" were commonly reported. There is therefore reason for believing that many of the suicides were emotionally ill within the last month of their life. Of the 689, 122 (17.7%) had been referred to a psychiatrist, and 92 of these had been in a mental hospital, nearly two-thirds of them within their last year of life. The time which elapsed between their discharge from hospital and their death is shown in Table I.

TABLE I.—*Time Which Elapsed Between Discharge from Hospital and Death*

Time	No. of Suicides	Average No. per Month (Up to 1 Year)
<1 month	23	23
1 month to 6 months ..	26	5·2
6 months to 1 year ..	10	1·7
Over 1 year	33	
Total	92	

The largest group of suicides died more than a year after they left hospital, but these of course included persons discharged from hospital several years before. There was a very rapid decrease in the number of ex-patient suicides with the passage of time after their discharge. The most dangerous time was immediately after discharge. This finding agrees with the observations of Shneidman and Farberow (1957).

Among the 881 suicides only 46 (5.2%) were reported to have made an earlier attempt; it has been remarked elsewhere (Stengel, 1952) that most people who commit suicide are successful at the first attempt. Some of the suicides had shown the clearest signs of profound depression. Though the numbers of these are probably not complete they are still a substantial part of the total number: 81 (9%) had expressed a wish for death, and 55 of them had said that they intended to kill themselves.

Condition Immediately Before Death

The demeanour and behaviour of the suicides when they were last seen alive were routinely recorded in the inquest reports. The witnesses had been nearly always in close contact with the suicides, and a number of corroborative accounts by different and sometimes unconnected observers gave a picture which was probably substantially reliable. The state described was that which was apparent at most a few hours, and often only a few minutes, before death.

It is possible to group in a few categories the reported conditions just before death. These are shown in Table II.

As might be expected the largest group were depressed when they were last seen alive. The group comprising those emotionally disturbed, though not depressed, included a few who were clearly paranoid. Some were worried, mostly by domestic difficulties. Some had quarrelled immediately before their death. These last were of the kind described by Batchelor (1954). Their death was an angry impulsive response to frustration, and their attitude was typified by a

TABLE II.—*Numbers of Suicides, by Sexes, and Their Observed Condition Just Before Death*

Condition	Males	Females	Total	%
Depressed	210	131	341	38·7
Emotionally disturbed*	89	45	134	15·2
Drunk	17	3	20	2·3
Normal	215	91	306	34·7
Unknown	58	22	80	9·0
Total	589	292	881	99·9

* Emotionally disturbed refers to suicides who were described in various terms which indicated abnormality, but who were not apparently depressed. These were irritable, angry, worried, afraid, suspicious.

sensitive and determined 20-year-old nurse who considered that she had been unjustly treated by a nursing sister, immediately tendered her resignation, and retired to kill herself with phenobarbitone. When she was last seen alive she was "not miserable but annoyed."

The 2.3% who were drunk at the time of their death is a small proportion by comparison with the 10% reported by Stengel and Cook (1958), but the latters' suicides occurred in an exclusively urban population.

An impressive fact is the number of suicides who were said to have appeared normal immediately before their death. Only 46 of these, however, were reported to have appeared always normal and to have been completely inexplicable suicides. Most of this normal group, 260, had apparently improved just before their death. Of them it was recorded, "He was always moody, but he was normal when he went out" (to hang himself); "He ate a hearty breakfast—a change for him!" Twelve of those called normal were perhaps elated and were described as: "In high spirits"; "I never saw him so well." This corresponds with clinical experience that the stage of early apparent improvement in a depression is potentially a most dangerous time. A decision to die means a solution of problems, for an intending suicide is already detached from the difficulties which had beset him. Dr. Samuel Johnson, speaking of "the melancholy end of a gentleman who had destroyed himself," said, "I have often thought, that after a man has taken the resolution to kill himself, it is not courage in him to do anything, however desperate, because he has nothing to fear. . . . When Eustace Budgel was walking down to the Thames, determined to drown himself, he might, if he pleased, without any apprehension of danger, have turned aside and first set fire to St. James's Palace" (Boswell, 1851).

Among the 306 suicides who had appeared normal just before their death, did there occur a sudden suicidal impulse after they were last seen alive, or did there already lie beneath a calm exterior an intention to die? Many of the suicides had appeared well only a minute or two before their death. If, in these, there had been no suicidal intent when they last spoke to their relatives or friends, then the final change in their mental state must have been dramatic and almost instantaneous. The probability is that the intention to die was already there.

Several of the suicides in this study were certainly preparing to die when they were last seen alive and apparently well. Some had already written farewell letters when their relatives last saw them and found them to be normal. Typical of those who appeared unconcerned while they planned suicide was a woman of 64 who appeared severely depressed on the day before her death, when she said, "Have a good Christmas; I won't be with you." The next morning, at 7 o'clock she told her husband, "I'm pretty good this morning." At 8 a.m. she walked from her home toward the river with no other likely motive than the one which later was apparent. On her way she was joined by, and talked with, a neighbour, to whom she appeared completely normal. As they exchanged trivial conversation she glanced at the river from time to time, and when her companion left her she walked into it.

The frequency with which the suicides had appeared depressed, emotionally disturbed, or normal just before death increased or decreased with advancing years. This is shown in Table III.

TABLE III.—*Condition of the Suicides Just Before Death, by Age-groups*

Condition	<30 Years		30–59 Years		60+ Years		Total
	No.	%	No.	%	No.	%	
Depressed	13	20·6	160	34·3	168	47·9	341
Emotionally disturbed	18	28·6	81	17·4	35	10·0	134
Drunk	1	1·6	16	3·4	3	0·9	20
Normal	26	41·3	165	35·6	115	32·7	306
Unknown	5	7·9	45	9·6	30	8·5	80
Total	63	100·0	467	100·3	351	100·0	881

Depression was proportionately more common among suicides aged 60 and over than among those under 30, and occupied an intermediate position in the intermediate age-group. Both emotionally disturbed and normal states were proportionately more common among suicides under 30 years old than among those 60 and over, and occupied an intermediate position in the intermediate age-group. At 60 and over there was a higher proportion of depressed suicides than of any other category. Under the age of 30 there was a higher proportion of apparently normal or emotionally disturbed suicides. The frequency with which depression was reported in those aged 60 and over agrees with the statements of other writers regarding the association between old age and depression (Batchelor and Napier, 1953; O'Neal *et al.*, 1956; Roth and Morrissey, 1952).

Evidence Given by Suicide Notes Regarding the Mental State

Of the 881 suicides, 136 left suicide notes: 83 were written by males, and 53 by females (14.1% of the male suicides and 18.2% of the female suicides). Suicide notes were written relatively more often by the younger suicides than by the older. Their numbers were: ages up to 29 years, 12 notes (19% of the age-group); ages 30 to 59, 82 notes (17% of the age-group); ages 60 and over, 42 notes (12% of the age-group).

Many of the notes showed that their writers on the point of death still desired the good opinion of their survivors, and felt impelled to explain and justify their act. More than half (79) of the notes gave a "reason for suicide"—usually an inability any longer to tolerate a painful situation. Only one of the notes showed simply an indifference to life. Among the older suicides physical illness or believed physical illness was much more commonly the "reason" than among the younger. Of 28 who complained of illness only four were under the age of 60. Only nine notes mentioned business or financial difficulties.

The instructions sometimes left by suicides regarding the management of their affairs revealed an attachment

to the things of this world which contrasts oddly with a wish to die. There were 30 notes which contained such instructions. In a different category were the 14 notes which were prominently displayed to warn others against gas or electricity, or to reduce their distress by telling them to call for help before entering the house.

Courbon (1934) remarked on the indifference to death which may be produced by the individual concept of it, and Zilboorg (1936) thought that the belief in after-life is one of the most powerful determinants of suicide. But though 79 notes explained what their writers were escaping from, only 30 gave any indication of what they believed they were going to. Two of these bade farewell in such terms that it appeared the separation was to be final; the other 28 showed a belief in a personal future in such phrases as "Till we meet again," or "I'll be watching over you." Though Zilboorg (1936) believed a desire to reunite with a dead loved one was a potent motive for suicide, only three notes revealed such a motive.

In 16 notes it was apparent that the prime motive for the writers' suicide was malice. For each of these 16 suicides there was evidence of a recent quarrel, of psychopathic behaviour, or of alcoholism. One such suicide was a typical example of the impulsive psychopathic gesture described by Batchelor (1954) which might follow a quarrel or an injury and which is intended to punish the survivors. A man aged 32, discharged from the Army as a psychopathic personality, had been drinking excessively for some days with his brother. He was found drowned in a dock, having been drunk when he was last seen alive. He was not known to have threatened suicide, and his death would have been meaningless and probably dismissed as accidental if it were not for a derisive note found in his pocket which said, "Well, Bill, [his brother] laugh this off. I got on your nerves, what a laugh. You got on mine too. Hope you enjoy the funeral, ha ha. Don't forget to wear a flower, ha ha." No quarrel was admitted by the brother, but the remark "I got on your nerves" suggests that the accusation had recently been made.

The contents of the suicide notes tended to vary with the age of the writers. References to the hereafter were made proportionately much more often in notes written by suicides over 60 years old. They occurred in 14 (33.3%) of the notes written by that age-group and in 16 (17%) of the notes written by those under 60. Instructions regarding the management of affairs occurred in the same proportions as those mentioned above: 33.3% for those 60 and over and 17% for those under 60. Directions intended to protect survivors from danger or distress were also proportionately much commoner in the notes written by the older than in those written by the younger group: 6 (15.3%) for the older, and 8 (8.5%) for the younger.

The relative frequencies were reversed, however, for notes containing wounding and malicious messages. Such messages occurred in 3 (7.1%) of the notes written by those aged 60 and over, and in 13 (13.8%) of those written by those under 60. Only 11 of the suicides were under the age of 20 years, and three of these (two schoolboys of 14 and a girl of 17) left notes. The contents of these notes were reproachful and self-pitying, and said, "I'm sick of slaving for Dad, a mean ungrateful man," and "Now you'll be able to get all you wanted to."

Summary and Conclusions

With a view to finding whether the number of suicides might be reduced immediately by early medical recognition and treatment rather than by longer-term social measures, the coroners' records were examined for the 881 suicides which occurred in Wales in the five years 1951–5. Information was collected regarding the presence of signs of emotional disturbance, the frequency of danger signals which called for immediate preventive action, the number of suicides who had received medical attention, and the number who died despite their having received psychiatric treatment.

As regards the earlier signs of emotional disturbance, 78% had been treated by their doctor for symptoms which appeared often to have been related to psychiatric disorders. This is a much higher proportion than the 40% who had received medical attention in the group of suicides reported by Parnell and Skottowe (1957). Nine per cent. had openly wished for death or had said that they intended to kill themselves.

During their last hours 39% appeared depressed, and most of the 35% who appeared normal had been depressed previously. Smaller proportions were drunk or emotionally disturbed though not depressed. Depression immediately before death was reported most commonly in suicides aged 60 and over. A normal demeanour just before death was reported most commonly in suicides below the age of 30. The normal and emotionally disturbed states became less common with advancing age, while depression became more common.

The contents of the suicide notes tended to vary with the age of the suicides and reflected the demeanour of the different age-groups. Complaints of physical illness, references to the hereafter, and a concern for relatives were most usual in the notes written by the older suicides, the age-group in which depression was commonest; while messages showing wounding and malicious motives were found more often in notes written by the younger group, the age-group in which normal demeanour and emotional disturbances other than depression predominated.

In most of the suicides, therefore, there had existed signs of emotional abnormality which differed to some extent according to age and which varied in degree from complaints of "nerves" to suicidal threats.

Many of those who had been emotionally disturbed for a time which would have made intervention possible did not receive psychiatric treatment, for, though 78% had been attended by their doctor, only 18% of these had been referred to a psychiatrist. It is not suggested that these were all recognizable as potential suicides, but it is likely that a substantial number showed a need for psychiatric attention, and certainly wishes for death and threats of suicide did not always receive the attention they deserved.

It must be conceded that psychiatric treatment cannot prevent all suicides. The explosive and sudden suicide probably cannot be prevented, and it is doubtful whether medical intervention can save a really determined would-be suicide. The fact that 92 committed suicide despite their having been treated in a mental hospital might call into question the value of such treatment, but this number must be contrasted with the very large number of attempted suicides and potentially suicidal patients who were treated in mental

hospitals throughout Wales in the five years and who did not subsequently commit suicide. One important fact which the death of these 92 ex-mental-hospital patients does demonstrate is the need for vigilance by family doctors and psychiatric out-patient clinics in the months immediately after patients' discharge from hospital, for nearly two-thirds of the 92 died within a year of their discharge.

The examination of the 881 suicides suggests that the number of suicides could be reduced now by medical means; for (1) signs of emotional abnormality were commonly present for some time before death, (2) comparatively few had received psychiatric treatment, (3) signs of profound depression sometimes did not receive the urgent attention which would have been given to a medical or surgical emergency, and (4) comparatively few of the large population "at risk" in mental hospitals later commit suicide.

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REFERENCES

Batchelor, I. R. C. (1954). *Brit. med. J.*, **1**, 1342.
—— and Napier, M. B. (1953). Ibid., **2**, 1186.
Boswell, J. (1851). *The Life of Samuel Johnson*, Vol. 2, p. 147. National Illustrated Library, London.
Courbon, P. (1934). *Ann. Méd.-psychol.*, **92**, (ii), 384.
O'Neal, P., Robins, E., and Schmidt, E. H. (1956). *A.M.A. Arch. Neurol. Psychiat.*, **75**, 275.
Parnell, R. W., and Skottowe, I. (1957). *Lancet*, **1**, 206.
Roth, M., and Morrissey, J. D. (1952). *J. ment. Sci.*, **98**, 66.
Sainsbury, P. (1955). *Suicide in London*. Maudsley Monographs No. 1. Chapman and Hall, London.
Shneidman, E. S., and Farberow, N. L. (1957). *Clues to Suicide*, p. 5. McGraw-Hill Book Company Inc., New York.
Stengel, E. (1952). *Proc. roy. Soc. Med.*, **45**, 613.
—— and Cook, N. G. (1958). *Attempted Suicide*, p. 104. Maudsley Monograph No. 4. Chapman and Hall, London.
Swinscow, D. (1951). *Brit. med. J.*, **1**, 1417.
Zilboorg, G. (1936). *Amer. J. Psychiat.*, **92**, 1346.

UROPEPSINOGEN LEVEL IN POST-GASTRECTOMY CASES

BY

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The existence of a pepsin-like proteolytic enzyme in the urine has been known for nearly a century (Brücke, 1861). In 1890 Bendersky named the substance uropepsin, but the final proof of its identity came from experiments by Mirsky *et al.* (1948). That urinary pensinogen excretion quantitatively reflects the gastric pepsin output was shown satisfactorily by Janowitz and Hollander (1950) and Spiro *et al.* (1950), who also showed it as an index of adrenocorticoid activity. Attempts to utilize its assay for diagnostic purposes in cases of gastric and duodenal ulcer were made by Podore *et al.* (1948), Mirsky *et al.* (1948), Janowitz *et al.* (1950), and Hirschowitz (1953).

According to Sircus (1954), "the measurement of the excretion of uropepsinogen has the advantage over test meals of providing a quantitative estimation of peptic-cell function with the minimum of disturbance of the patient and without the aid of artificial stimuli." It was for this reason that a series of 90 patients on whom gastrectomy had been performed, on account of peptic ulceration, between January, 1954, and October, 1956, were followed up. The uropepsinogen level was assayed in 75 cases on the average 18 months post-operatively, employing Fawcett's (1951) adaptation of the methods of Bucher (1947) and Mirsky *et al.* (1948) using the substrate recommended by Orringer *et al.* (1950).

The results are expressed as the number of units of uropepsinogen per hour (U.P./hr.), where a unit of uropepsin is the same as that of Mirsky *et al.* (1948), who defined it as "that quantity which, during a 10-minute incubation of the standard assay, releases 1 mg. of 'tyrosine-like' substance," and correction for dilution after the 30-minute incubation period being 1 unit/100 ml. of urine≡0.0015 mg. of tyrosine.

Method.—Each patient was instructed how to collect a full 24-hour specimen of urine—namely, voiding the bladder at 8 a.m. and discarding the sample; then collecting all urine until 8 a.m. next day, when the bladder is again voided—this time the sample being kept. These 24-hour specimens are, however, not always accurate in spite of detailed instructions to patients; the uropepsinogen level was estimated in 75 of the 90 patients studied.

Results

The uropepsinogen level varied from 0 to 5.8 U.P./hr., and we were able to divide the 75 cases into the following groups clinically.

Good Surgical Result but General Health Poor (8 cases).—In this group the uropepsinogen level was found to be less than 0.7 U.P./hr. in all cases. Two patients had contracted phthisis and one pernicious anaemia, four complained of an ill-diagnosed ill-health showing a mild microcytic anaemia, and only one showed radiological evidence of stomal ulceration. No patient complained of dyspepsia.

Good Result (48 cases).—Apart from two who were unreliable witnesses, the rest stated that they had never felt better, and the uropepsinogen levels in this group were between 0.8 and 3.0 U.P./hr.

Good with Occasional Symptoms (9 cases).—All these patients admitted to occasional dyspepsia in spite of careful diet, but in none was there any radiological evidence of stomal ulceration. Uropepsinogen level in this group was between 3.1 and 4.1 U.P./hr.

Slight Symptoms (7 cases).—All admitted having flatulence with occasional severe dyspepsia, and in four there was radiological evidence of stomal ulceration. The uropepsinogen level was 4.2–5.1 U.P./hr.

Dyspepsia (3 cases).—These three noticed their symptoms had returned very quickly after surgery; their uropepsinogen level was in excess of 5.2 U.P./hr., but in none was it more than 5.8 U.P./hr.

Summary

From a series of 90 post-gastrectomy cases, uropepsinogen estimation was carried out in 75 cases on an average of 18 months after operation. There was a close correspondence between the clinical results of gastrectomy and the uropepsinogen level. Therefore it is suggested that if a more accurate method of collecting 24-hour specimens of urine were available the uropepsin-

ogen assay would be a good method of estimating the success of gastrectomy.

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REFERENCES

Bendersky, J. (1890). *Virchows Arch. Path. Anat.*, **121**, 554.
Brücke, E. (1861). *S.-B. Akad. Wiss. Wien. math.-nat. Kl.*, Abt. 2, **43**, 618.
Bucher, G. R. (1947). *Gastroenterology*, **8**, 627.
Fawcett, J. K. (1951). *J. med. Lab. Tech.*, **9**, 170.
Hirschowitz, B. I. (1953). *Lancet*, **1**, 66.
Janowitz, H. D., and Hollander, F. (1950). *Fed. Proc.*, **9**, 67.
—— Levy, M. H., and Hollander, F. (1950). *Amer. J. med. Sci.*, **220**, 679.
Mirsky, I. A., Block, S., Osher, S., and Broh-Kahn, R. H. (1948). *J. clin. Invest.*, **27**, 818.
Orringer, D., Lauber, F. U., and Hollander, F. (1950). *Science*, **111**, 88.
Podore, C. J., Broh-Kahn, R. H., and Mirsky, I. A. (1948). *J. clin. Invest.*, **27**, 834.
Sircus, W. (1954). *Quart. J. Med.*, **23**, 291.
Spiro, H. M., Reifenstein, R. W., and Gray, S. J. (1950). *J. Lab. clin. Med.*, **35**, 899.

HAEMORRHAGIC CHICKEN-POX

TWO FATAL CASES

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Chicken-pox is a benign disease with minimal complications and a very low mortality. Death occasionally supervenes as a result of one of the following complications: sepsis; haemorrhagic manifestations; renal, neurological, or haematological sequelae (Lander, 1955; McLachlan, 1957). Recently several fatal cases of haemorrhagic chicken-pox have been reported after cortisone therapy (Haggerty and Eley, 1956; Bernheim *et al.*, 1956; Nichols, 1957). It is also well known that severe infections are common in association with diseases of lymphoid tissue.

Two fatal cases of haemorrhagic chicken-pox are here reported: one patient had been treated with cortisone, and the other was a known case of Hodgkin's disease with enlargement of the spleen and lymph nodes.

Case 1

The patient, a boy aged 13, was admitted to hospital on February 5, 1958. A diagnosis of tuberculous meningitis was made, and treatment was immediately started with intramuscular and intrathecal streptomycin along with isoniazid and cortisone. He was given 100 mg. of cortisone intramuscularly each day for two days, followed by 50 mg. three times a day by mouth for two days, after which the dose was increased to 50 mg. four times a day.

On February 24 four vesicles appeared on his trunk and within a few hours the rash had covered the whole body and chicken-pox was diagnosed. Several cases of this disease had recently occurred in his school and all had taken a normal course. On February 27 he passed blood-stained urine, and had a haematemesis and an epistaxis. The rash became extensively haemorrhagic, and he died on February 28. Permission for a necropsy was not obtained.

Case 2

This patient was a woman aged 34. Hodgkin's disease had been diagnosed three years previously and her general condition had been satisfactory after radiotherapy. On January 17, 1959, she felt unwell and discovered "spots" on her trunk. Her family doctor diagnosed chicken-pox, and it was noted that another member of the household had had an attack of herpes zoster at the end of December, 1958. On January 20 the rash was very extensive, and one of us (A. M. N.) was consulted and confirmed the diagnosis of chicken-pox. Two days later the patient was very distressed, with a poor colour and rapid respirations. Signs of consolidation were found over the right lung and she was sent into the isolation hospital. On admission her general condition was poor. The extremities were cold and blue; temperature 101° F. (38.3° C.); respirations 46; pulse 130 a minute. The trunk was covered with a haemorrhagic papular eruption, which was also present on the face. The forearms and legs were relatively free of lesions. Consolidation of the right lung was confirmed. In spite of active treatment she collapsed and died at 10.30 p.m. the same day.

A post-mortem examination was performed 16 hours after death (R. W. P. J.). The body was that of a slim well-nourished young woman. There was an extensive confluent haemorrhagic vesiculo-papular eruption involving the trunk and face. Lesions were scanty on the arms and thighs, and there were none on the hands or below the knees. Similar lesions were found in the oesophagus. The trachea and main bronchi contained mucopus. There were many subpleural haemorrhages, and both lungs showed bronchopneumonic consolidation. The spleen was greatly enlarged, weighing 40 oz. (1,135 g.), and was extensively infiltrated by greyish neoplastic tissue. There were many enlarged glands along both sides of the abdominal aorta and in the mediastinum. The liver was pale and soft. Serum and scrapings from the skin vesicles were tested for smallpox; the complement-fixation test and egg cultures were negative for the variola-vaccinia group viruses.

Discussion

Cortisone may have an untoward effect on infectious diseases, including bacterial, fungal, and virus infections, and it has been shown that the drug inhibits antibody production (Haggerty and Eley, 1956). Infections occur with great frequency along with diseases of lymphoid tissue, and agammaglobulinaemia may occur in disease of the reticulo-endothelial system such as Hodgkin's disease (MacCallum, 1959; Kaplan and Smithers, 1959).

Chicken-pox is normally such a mild disease that it is apt to be regarded as of little importance, but severe and even fatal cases have been described in patients undergoing cortisone therapy (Shee and Fehrsen, 1953; Haggerty and Eley, 1956; Bernheim *et al.*, 1956). In these cases the cortisone had presumably inhibited the normal production of antibodies. Haggerty and Eley state that in some cases of chicken-pox cortisone has no apparent ill effect, but in others the skin manifestations are unusually severe, and they had seen two children who died in a state of shock.

When confluent haemorrhagic vesicular eruptions are encountered, smallpox must be considered as a possible diagnosis, but in the two cases described above the diagnosis of haemorrhagic chicken-pox was confidently made on clinical grounds and confirmed by subsequent events. It is suggested that in these two cases the

antibody response to the varicella virus had been modified—by cortisone therapy in Case 1 and by the infiltration of the reticulo-endothelial system in Case 2. It appears that chicken-pox may be a very serious disease in patients who are either undergoing cortisone therapy or who are suffering from a disease of the lymphoid tissue. If a patient on cortisone develops chicken-pox, serious consideration should be given to the advisability of withdrawing the drug, or at least reducing the dose; and it may also be worth while giving the patient convalescent varicella serum (Nichols, 1957).

Summary and Conclusions

Two fatal cases of haemorrhagic chicken-pox are described. The antibody mechanism had been upset in one by cortisone therapy, in the other by neoplastic infiltration of lymphoid tissue. It may be necessary to modify cortisone therapy if chicken-pox supervenes.

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References

Bernheim, M., Larbre, F., Mouriquand, Cl., and Germain, D. (1956) *Pédiatrie* **11**, 920.
Haggerty, R. J., and Eley, R. C. (1956). *Pediatrics*, **18**, 160.
Kaplan, H. S., and Smithers, D. W. (1959). *Lancet*, **2**, 1.
Lander, H. (1955) *J. Path. Bact.*, **70**, 157.
MacCallum, F. O. (1959). *Proc. roy. Soc. Med.*, **52**, 135.
McLachlan, I. M. (1957). *Lancet*, **2**, 492.
Nichols, W. W. (1957). *A.M.A. J. Dis. Child.*, **94**, 219.
Shee, J. C., and Fehrsen, P. (1953). *Brit. med. J.*, **2**, 82.

Medical Memoranda

A Case of Locked Twins

Cases of locked twins would seem to be rare enough to warrant publication. The incidence is quoted as 1 in 1,000 twin labours (Nissen, 1958), and in addition to its rarity it is a disconcerting hazard, occurring as it usually does late in the second stage of labour.

Lawrence (1949) classified the various types of foetal interlocking and the high incidence in cases of twin labour with the breech–vertex combination, as was the case in this instance.

Case Report

An unmarried primigravida aged 37 was admitted as an emergency case in labour with a twin pregnancy of 37 weeks' duration. On examination the membranes were intact, the first twin was in the left sacro-anterior position, and the second twin presented as a vertex. Both foetal hearts were easily audible and of regular rhythm; uterine contractions were regular and frequent.

Labour progressed uneventfully, and a vaginal examination after spontaneous rupture of the membranes confirmed the presentation of the first twin; the cervix was dilated three fingerbreadths, and no loop of umbilical cord was palpable.

After full dilatation of the cervix, with descent of the breech, medical aid was summoned. On arrival both legs were visible at the introitus, uterine contractions were strong and regular, and there was no evidence of foetal or maternal distress. Episiotomy, after local perineal infiltration, aided delivery of the buttocks. The body as far as the umbilicus was allowed to deliver spontaneously, a loop of cord was brought down, and the arms were delivered without difficulty.

Further progress was slow despite traction on the buttocks and suprapubic pressure. This was surprising, as the baby was small and the pelvis known to be of adequate size. Vaginal examination then revealed the vertex of the second twin firmly impacted with the aftercoming head of the first twin in the pelvic cavity. Manual disimpaction under general anaesthesia was attempted but failed. Decapitation of the first twin was then performed, as it showed no signs of life. The decapitation, using strong curved scissors, was facilitated by shoulder traction. Removal of the body of the first twin then allowed the easier disimpaction of the severed free head.

The lie and presentation of the second twin was confirmed, the membranes were artificially ruptured, and a living female child of 4 lb. 1 oz. (1,840 g.) was delivered by forceps extraction. Manual extraction of the free head, by combined suprapubic pressure and traction by a finger in the mouth, proved relatively easy. Delivery of the placenta was performed manually, after the injection of 0.25 mg. of ergometrine intravenously. The progress of both mother and baby was satisfactory.

Comment

The cause of this rare complication has not been satisfactorily explained; none of the various theories are entirely satisfactory, but undoubtedly the element of chance plays a great part.

The diagnosis can usually be made only late in the second stage of labour, but it is suggested that this complication should be considered in any twin labour where there is failure of descent of the presenting part in the presence of good uterine contractions, an adequate pelvis, and no evidence to suggest a hydrocephalic monster, but particularly in cases with a breech–vertex combination.

The decapitation of the first twin in this case was an unavoidable expedient, but it might have been prevented by earlier careful vaginal examination, prior to traction on the buttocks with fundal pressure, which resulted in firm impaction and did not allow manual disengagement.

Suggestions regarding treatment must necessarily be retrospective, as no large single series of cases is available on which to base a uniform approach. The treatment, however, depends on the type of locking, the duration of the locking, and the level in the pelvis at which locking has developed. Cases with interlocking of the fore-coming heads in the pelvic brim are best treated by caesarean section (Dawson, 1936). Usually delivery by the vaginal route must necessarily be performed. Manual disimpaction may prove successful in the early cases where there has been no traction on the buttocks, and when the locking has occurred at the level of the ischial spines and has been of short duration. Later on, some form of destructive operation to achieve delivery is necessary, as in the case reported.

The prognosis for the first twin is very poor. Nissen (1958) noted a 60% mortality in all cases reported in the literature. The second twin has a far better outlook, but there should be no delay in the delivery, either by forceps extraction or by breech extraction.

I thank Mr. W. H. Peek for his help and for permission to publish this case.

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References

Dawson, J. B. (1936). *J. Obstet. Gynaec. Brit. Emp.*, **43**, 507.
Lawrence, R. F. (1949). Ibid., **56**, 58.
Nissen, E. D. (1958). *Obstet. and Gynec.*, **11**, 514.

Washing-machine and Electric Wringer: A Domestic Hazard to Children

Mechanical devices in the home, particularly those which are electrically driven, carry occasional risks. The admittance of two patients with injuries from mangles attached to washing-machines to the paediatric department of one hospital within a short time led us to believe that similar accidents may not be infrequent, and the two cases present so many similarities that note should be made of them.

CASE 1

A boy aged 4 years caught his left arm between the rollers of the electric wringer attached to his mother's washing-machine on November 7, 1958. The machine had inadvertently been left running unattended. His arm was drawn in as far as the elbow, and the rollers continued to turn until his mother found and released him, a period estimated at four minutes.

On admission to hospital one week later he was found to have a clear well-demonstrated friction burn, obviously of full skin-thickness, approximately 3 by 2 in. (7.5 by 5 cm.) on the antero-medial aspect of his left elbow. At operation on November 18 this area was excised, and covered with split skin obtained from the left thigh.

This graft took successfully (Fig. 1), and when the boy was finally seen in the out-patients department on February 2, 1959, the area was well healed, with only a small amount of keloid formation. He had full function, and there was no evidence of contracture.

CASE 2

A girl aged 8½ years was admitted on January 12, 1959. Two days previously she had caught her left arm in the electric wringer of her mother's washing-machine, which had been running unattended. In this case also the rollers continued to turn and her arm was drawn in as far as the elbow, where it remained until her mother switched off the machine a minute or so later.

The patient had a very well demarcated friction burn approximately 3 by 2 in. (7.5 by 5 cm.) on the antero-medial aspect (Fig. 2) of the elbow with considerable surrounding bruising and oedema. There was also marked weakness of flexion and extension of the fingers, with impairment of skin sensation along the ulnar border of the hand. Flexion and extension of the wrist were full.

At operation on January 23, after the swelling had largely subsided, the burned area was excised, and covered with split skin obtained from the left thigh. The whole skin was coagulated and beneath it was necrotic subcutaneous fat and blood-stained fluid. This graft took successfully and healing was rapid.

Recovery of finger movements was slow, however, and wasting of thenar and hypothenar muscles became evident. She was thought to have median and ulnar nerve palsies, and has been receiving physiotherapy.

When last seen in the out-patient department there was evidence of commencing recovery from these nerve lesions, while the burned area was completely healed.

COMMENT

Both cases show that these friction burns are produced very rapidly and in a short time involve the full thickness of the skin. Only the area actually in contact with the roller is affected and the lesions are very sharply defined. The destruction being very rapid, pain was not severe. The similarity of the situation of the burns is very easily explained. The hand is caught between the rollers in the prone position and the arm is drawn in as far as the elbow, being stopped then as the child is pulled against the washing-machine. The lower roller produces the damage as it rotates in contact with the inner part of the elbow. The drive is on the lower roller only in the types of wringer involved. The upper is idle and can

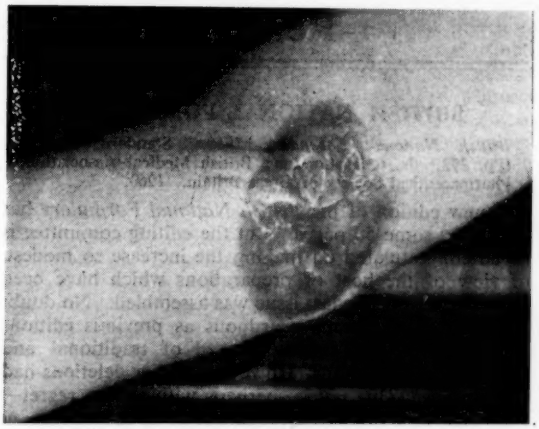

FIG. 1.—Case 1. Grafted area healed.

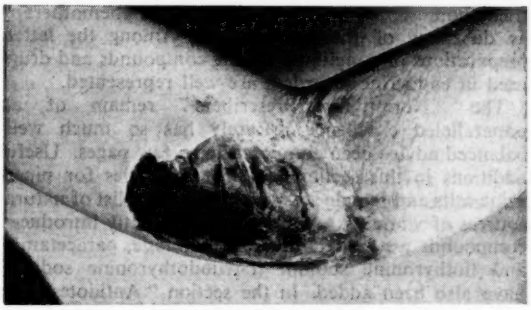

FIG. 2.—Case 2. Coagulated burnt skin at time of admission to hospital.

do no harm. In neither case was it appreciated at once that the full thickness of the skin was involved, and admission to hospital was delayed. The older child received severe soft-tissue damage as well, which may be explained by the larger size of her arm, and had the machine gone on for a longer time much worse damage might have been produced. As regards the skin, these cases were ideal for early excision and grafting on account of the very sharp demarcation of the lesions, and the absence of sepsis.

The washing-machine with electrically driven wringer is becoming increasingly popular, and, with the present relaxation of hire-purchase regulations, is likely to be found in more and more households. To avoid such accidents, both of which occurred when the mother was out of the room, the machines should never be left running unattended when children have access to them until or unless a foolproof safety device is provided. Similar machines in a factory would have to be guarded. It is not within our province to suggest technical details, but in a small household it is impossible for the children to be kept away from the washing-machine, and the mother must on occasion be called away to attend to other matters. A "dead man's handle" type of switch, which would go into the off position as soon as the person operating the machine leaves, might make the device safer. It must be realized, however, that it is almost beyond the wit of man to defeat a determinedly inquisitive child.

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Reviews

BRITISH NATIONAL FORMULARY

British National Formulary 1960. Standard edition. (Pp. 272. 7s. 6d.) London: British Medical Association, Pharmaceutical Society of Great Britain. 1960.

The new edition of the *British National Formulary* has grown by some 50 pages. But the editing committee is to be congratulated on making the increase so modest, in view of the host of preparations which have been introduced since the last issue was assembled. No doubt their task was the more arduous as previous editions have already been largely pruned of traditional and little-used prescriptions. However, further deletions had to be made. One notes—perhaps with a little regret—that such time-honoured preparations as tab. ipecac. et opii and mist. gelsem. et hyoscy. co. have gone. Other omissions like that of inj. neoarsphenamin. and tab. trisulphon. signify welcome advances in chemotherapy as do many of the "additions." Among the latter, preparations of ganglion-blocking compounds and drugs used in endocrine disorders are well represented.

The "Notes for Prescribers" remain of an unparalleled excellence. Rarely has so much well-balanced advice been composed in so few pages. Useful additions in this section are dose schedules for piperazine salts and female sex hormones, and a list of natural sources of vitamins. Notes on such recently introduced compounds as, for example, glutethimide, paracetamol, and liothyronine sodium (L-triiodothyronine sodium) have also been added. In the section "Antidotes" the use of sodium calciumedetate in poisoning with metals other than lead may be worth mentioning in the next edition. It may perhaps also be advisable in future to alter the heading of the section on antihistamines (p. 28) in order to be able to restrict this term to drugs which "protect the tissue receptors against the histamine which is released." The lists of proprietary preparations and of approved names has been considerably expanded, this should promote rational and economical prescribing.

The 1960 edition of the British *National Formulary* has maintained the high standard of previous editions and has—if possible—even surpassed it. It is difficult to see how any practitioner in Great Britain—and many other countries of the Commonwealth, for monographs on drugs used in tropical infections, for instance, are well represented—can avoid consulting this handy volume every day.

H. HELLER.

A CATALOGUE OF R.C.S.'s PORTRAITS

A Catalogue of the Portraits and Other Paintings, Drawings, and Sculpture in the Royal College of Surgeons of England. By William LeFanu. (Pp. 119+xii; illustrated. 30s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

During the hundred and sixty years of its existence the Royal College of Surgeons of England has accumulated a large number of valuable paintings, drawings, statues, and other valuables which are not so well known as they deserve to be. The last catalogue (by Sir Frederic Hallett) was published thirty years ago and has long been out of print. As the preface to this book states, the collection is "now for the first time described in its entirety." This is in itself a noteworthy achievement and it is enhanced by the numerous and beautifully reproduced illustrations. The descriptions, by Mr. LeFanu, are accurate and detailed, and provide many interesting and little-known facts. A copy of this book should be in the possession of everyone interested in the College. Moreover, there must be many lay persons, lovers of art if not of surgery, who would find much to interest them in this catalogue, and still more in the originals. It is worth consideration by the College whether it might be possible occasionally (say once or twice a year) to have a demonstration of some of these exhibits to which the general public might be admitted.

ZACHARY COPE.

HANDICAPPED CHILDREN

The Child with a Handicap. A Team Approach to His Care and Guidance. Edited by Edgar E. Martmer, M.D. (Pp. 409+xxiv; illustrated. 82s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

The disturbing estimate that 10% of all children to-day have in some degree some form of handicap and the certainty that the number of those who survive is increasing, stress the needs of affected children. Many will require more specialized assistance than their parents can give, whether the handicap be physical, mental, or emotional. It is clearly important for the doctor to know where and how such assistance can be obtained. Teamwork is essential in any programme of rehabilitation, and it is refreshing to note that the editor of this book is in no doubt that the most important member of the team is the child. He pleads for young people to be encouraged to consider training for one of the various activities—nursing, physiotherapy, medical technology, social service, for example—which are part of the team's work.

Under the captaincy of Dr. Martmer this book has been written by a team of experts, and the subject is covered interestingly and efficiently from the widest viewpoint and in a well-balanced way. All doctors would benefit from reading the opening chapter, which succinctly describes Dr. Wishik's 25-point creed. A mother's point of view is also excellently expressed in the next chapter. The non-medical members of the team have made contributions as important and helpful as the professional, and the total editing has been most effective. Not all will agree about the status allotted to the psychiatrist in the management of epileptic children and their parents, though the part he can play in helping handicapped children as a whole is universally accepted and is discussed throughout the book in excellent perspective. There are other chapters on the roles of the physician, parent, psychiatrist, social worker, teacher, adoption agencies, and geneticist; then follow the more specific problems of the children handicapped by any of 15 major disabilities. The final chapters are devoted to the guidance of parents, discipline, remedial materials, and community programmes. There is a bibliography.

This is a Charles C. Thomas production, which is a guarantee of its excellence, although it is unusual to find that misspellings such as assymetrical (p. 13), ductus arteriosis and Wasserman (p. 78), cholasia (p. 133), arthrogyroposis (p. 138), opthalmologist (p. 145), and a few other printing errors in the index have not been spotted. The book is published in this country by Blackwell, and is worthy of being read by all who are interested in handicapped children, and particularly by those in any way concerned with their care.

WILFRID GAISFORD.

THE SURVIVAL OF THE UNFIT

Long-term Illness. Management of the Chronically Ill Patient. Edited by Michael G. Wohl, M.D., F.A.C.P., with the collaboration of 79 contributing authors. (Pp. 748+xix. £5 19s.) Philadelphia, London: W. B. Saunders Company. 1959.

The development of effective treatment for acute episodes of infective illness in recent years has undoubtedly saved many lives, but an inevitable consequence of this therapeutic success has been the survival of an increasing number of individuals with chronic disease. It is not surprising, therefore, that textbooks concerned with the management of long-term illness should appear, and this massive and expensive volume is an encyclopaedia of American practice in this field.

In the preface we are reminded cheerfully of the words of Henry H. Kessler that "The mists of nineteenth centry fatalism towards chronic disease are being dispelled by the sun of hopefulness and usefulness." Mr. Kessler's optimism seems a little premature in the light of the conclusions drawn by most of the contributors—unless, of course, one shares the opinion of the writer (given on p. 623) who believes that a good general practitioner or paediatrician at the head of a therapeutic team can make chronic illness in a child not a tragedy to be endured but an enriching, rewarding, and maturing experience for himself, the young patient, and the family.

If that sort of sentimentality prevailed there would be little purpose in undertaking laborious research to prevent or cure chronic disease in children. Fortunately, the authors of most of the sections are much more objective in their approach and the book is a useful work of reference for the general practitioner on whom the principal burden of the management of chronic illness falls. If he consults it he will find many suggestions for the treatment of each separate condition. The fact that there are so many shows, of course, that none of them is completely effective. Nevertheless, some form of treatment may help the patients, and the catalogue of what is available is useful. To an English physician it was surprising to find that the treatment of chronic bronchitis receives but scanty attention in the section devoted to pulmonary emphysema. The National Health Service in this country is suspect on the other side of the Atlantic, but it does at least deliver us from the worries of the sympathetic physician in America who (apparently against his better judgment) seeks, by using artificial pneumothorax as a substitute, to spare his patient "the financial cost of pulmonary resection."

ARTHUR THOMSON.

R.A.F. PREVENTIVE MEDICINE

Air Ministry Handbook of Preventive Medicine. Second edition. (Pp. 418+xxix; illustrated. 40s.) London: Her Majesty's Stationery Office. 1959.

This is the second edition of a handbook first published in 1946 as a guide and reference volume for medical officers of the Royal Air Force. The first 12 chapters, which formed the matter of the original handbook, have been extensively revised and five new chapters and an introduction have been added. The introduction stresses the importance of preventive medicine and briefly outlines the basic organization of this discipline in the R.A.F. The new chapters are on such pertinent subjects as mental health, the occupational health of aircrew and of ground personnel, the toxic substances likely to be encountered on R.A.F. stations, and medical statistics. A chapter on radiation hazards is promised at a later date. In addition, there are four appendices, the first three dealing with routine hygiene inspections, the help that can be obtained from the laboratory in the control of infectious disease, and the prevention of alimentary infections, and the fourth containing a summary of international sanitary regulations.

The whole book is packed with information on a variety of subjects which affect the health of service personnel, and with which, unfortunately, the newly qualified doctor has often only a limited acquaintance. There are a few minor points to which objection might be taken. The R.A.F. Medical Service has set for itself such high standards of hygiene that it is a little disturbing to find a recommendation, without qualification of any sort, that crude sewage may be discharged directly into the sea. A knowledge of world climatic conditions is obviously of great importance, but does this justify the amount of space occupied by the subject—nearly a quarter of the bulk of the whole book—while the occupational health of aircrew is dismissed in a few pages?

In a book of this nature there are always points about which it is possible to cavil, and, with so much that is excellent, to do so is patently unfair. The handbook fills a very real need and will be of constant value, not only to newly joined medical officers, but also to the more senior, who will find it a source of assistance in many difficult situations. Both the original and the present editor are to be congratulated on having provided such a comprehensive and helpful volume.

ALAN ROOK.

TOXIC SUBSTANCES

Klinik und Therapie der Vergiftungen. By Sven Moeschlin. Third edition. (Pp. 655+xii; illustrated. DM. 59.) Stuttgart: Georg Thieme Verlag. 1959.

The first two editions of Dr. Moeschlin's *Klinik und Therapie der Vergiftungen* (Clinical and Therapeutic Aspects of Intoxications) laid special emphasis on the clinical and therapeutic aspects of pharmacological intoxications and less on industrial poisons. The third edition to some extent follows the same plan, but the descriptions of many of the toxic agents have been amplified and many new ones, especially those of industrial importance, have been added. Not only are a vast number of medicaments, drugs, and chemical compounds included, but also radioactive substances, poisonous plants and fungi, and even hormones and vitamins, with descriptions of their toxic effects, dosages, prophylaxis, and therapy.

To the English reader the chief drawback lies in the sections devoted to therapy. Many of the German proprietary preparations recommended are not widely known in this country, and valuable time might be lost in discovering their exact composition or where they could be obtained. On the other hand, some of Dr. Moeschlin's suggested remedies are remarkably simple, as, for example, the use of buttermilk for skin burns due to fluoric acid. Some of his statements may also seem at first sight somewhat controversial, but he almost invariably supports them with a statement of fact. For instance, he gives a warning that the ordinary

pedestrian is in danger of lead absorption from the exhaust gases of lead tetra ethyl, but goes on to state that in Basle the atmosphere in the streets contains 5 to 7 gamma of lead per cubic metre.

A unique and valuable feaure of the book is the last chapter on "Chief Symptoms of Poisoning," in which intoxications are treated in tabulated form according to the symptomatic aspect of each organ or system. An example of this arrangement may be taken from the sub-heading "Orthostatic Collapse" in the section "Circulatory Apparatus." This shows not only the wide scope and variety of the intoxications described, but also the difficulty, already referred to, with regard to proprietary preparations: "ecolid," "iproniazid," "mevasin," and "pendiomid" are listed as agents of this "ganglion-blocking" syndrome.

With such a wide range of subjects there is inevitably some over-simplification, but on the whole the most important facts are presented with an admirable conciseness which is of special value to those who need these facts without having to study the vast amount of research literature on which they are founded. Undoubtedly this monumental work will have a wide appeal as an indispensable reference book for clinicians, pharmacologists, and industrial toxicologists.

ETHEL BROWNING.

INBORN ERRORS OF METABOLISM

Maladies Héréditaires du Métabolisme Chez l'Enfant. By Maurice Lamy, Pierre Royer and Jean Frézal. Preface by Professor Robert Debré. (Pp. 259; illustrated. 3,600 fr.) Paris: Masson et Cie. 1959.

Dr. Maurice Lamy, Dr. Pierre Royal, and Dr. Jean Frézal have written a valuable new monograph on *Maladies Héréditaires du Métabolisme Chez L'Enfant.* Garrod would perhaps be quite surprised at the number of new "errors" discovered since his time. Indeed, one difficulty facing the authors must have been that reports of new disorders are rapidly appearing. This may in part explain why there is no mention of sucrosuria or abnormalities of fructose metabolism and why the only amino-acid disturbances are limited to Lowe's syndrome with a brief mention of the Hartnup syndrome (in the bibliography of phenylketonuria!) apart from a chapter devoted to alkaptonuria and to the phenylpyruvic-acid story in which the reviewer is sorry to see no mention of the work done at Great Ormond Street Hospital. The "maple syrup syndrome" has probably been missed out because it is one of the most recent to be reported. The inclusion of muco-viscidosis as a metabolic disorder is perhaps stretching the net too wide. The text is clearly written in easy French, well set out and with very good bibliographies at the end of each chapter. As with most French medical books there is regrettably no index. Professor Robert Debré contributes a preface.

ALAN MONCRIEFF.

Pain and Itch: Nervous Mechanisms, the proceedings of the Ciba Foundation's first study group, concerns itself, as the title suggests, not with the philosophical but with the material basis of pain. The inquiries, conducted by a distinguished international panel of scientists during a one-day study group, are necessarily highly technical, but they are lucidly presented and illustrated, and each of the eight papers is followed by a discussion. There are extensive references and an index. (J. & A. Churchill Ltd., 104, Gloucester Place, London, W.1; 120+viii pp., 12s. 6d.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Effects of Pollution on Living Material. Symposia of the Institute of Biology, No. 8. Edited by W. B. Yapp. (Pp. 154+xii; illustrated. 25s.) London: Institute of Biology. 1959.

La Fatigue. Physiologie, Psychologie, et Médecine Sociale. By Pierre Bugard. (Pp. 308; illustrated. NF. 32.) Paris: Masson et Cie. 1960.

Radiodiagnostic en Rhumatologie. 400 Images de Base. Travail du Centre de Rhumatologie Viggo-Petersen, Hôpital Lariboisière. By S. de Séze, Albert Djian, and Micheline Phankim-Chapuis. (Pp. 188. NF. 30.) Paris: Expansion Scientifique Française. 1960.

Selected Papers from the Institute of Cancer Research: Royal Cancer Hospital, and from the Royal Marsden Hospital, 1957. Cumulated List of Contents of Volumes 7 to 12, 1950–57. (Pp. 1,098+xx; illustrated.) London. 1959.

Surgeon Compassionate. The Story of Dr. William Marsden, M.D., M.R.C.S., Founder of the Royal Free and Royal Marsden Hospitals. By Frieda Sandwith. (Pp. 235+viii; illustrated. 21s.) London: Peter Davies. 1960.

Proceedings of the Fourth International Congress of Biochemistry, Vienna, September 1-6, 1958. General Editor: O. Hoffmann-Ostenhof. Volume XI. Symposium XI. ***Vitamin Metabolism.*** Edited by W. Umbreit and H. Molitor. (Pp. 373+xiii; illustrated. 73s.) London, New York, Paris, Los Angeles: Pergamon Press for the Organizers and the International Union of Biochemistry. 1960.

The Physical Health of Children. By Audrey Kelly. (Pp. 256. 3s. 6d.) Harmondsworth, Middlesex: Penguin Books. 1960.

The Surgery of Theodoric, ca. 1267. Translated from the Latin by Eldridge Campbell, M.D., and James Colton, M.A. Volume 2 (Books III and IV). (Pp. 233+xix. $5.50.) New York: Appleton-Century-Croîts, Inc. 1960.

Proceedings of the Fourth International Congress of Biochemistry, Vienna, September 1-6, 1958. General Editor: O. Hoffmann-Ostenhof. Volume VIII. Symposium VIII. ***Proteins.*** Edited by H. Neurath and H. Tuppy. (Pp. 258+xi; illustrated. 70s.) London, New York, Paris, Los Angeles: Pergamon Press for the Organizers and the International Union of Biochemistry. 1960.

Effect of Radiation on Human Heredity: Investigations of Areas of High Natural Radiation. First Report of the Expert Committee on Radiation. World Health Organization Technical Report Series, No. 166. (Pp. 47. 1s. 9d.) Geneva: World Health Organization. London: H.M. Stationery Office. 1959.

The General Practitioner and the Effectiveness of His Share in the Care of Health. By Dr. Y. van der Wielen. Foreword by Professor R. Hornstra. (Pp. 340.) Assen: Van Gorcum and Co. N.V. 1960.

Practical Electrotherapy for Physiotherapists. By Brenda Savage, M.Sc., M.C.S.P.(Teacher's Certificates). (Pp. 296; illustrated. 30s.) London: Faber and Faber, Ltd. 1960.

In Place of Parents. A Study of Foster Care. By Gordon Trasler, Ph.D. (Pp. 248+viii. 25s.) London: Routledge and Kegan Paul. New York: The Humanities Press. 1960.

Heritable Disorders of Connective Tissue. By Victor A. McKusick, M.D. Second edition. (Pp. 333; illustrated. 90s.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1960.

Atlas of Bacterial Flagellation. By Einar Leifson. (Pp. 171; illustrated. $7.) New York and London: Academic Press. 1960.

Polysaccharides in Biology. Transactions of the Fourth Conference, May 21-23, 1958, Princeton, N.J. Edited by Georg F. Springer, M.D. (Pp. 326; illustrated. $5.95.) New York: Josiah Macy, Jr., Foundation. 1959.

The Health of Business Executives. Transactions of a One-Day Conference held in the Royal Festival Hall, London, November 20, 1959. (Pp. 126. 15s.) London: Chest and Heart Association. 1960.

A Short Synopsis of Human Protozoology and Helmintholcgy. By L. R. S. Macfarlane, O.B.E., M.D., M.A., D.P.H., Brigadier. Illustrated by R. M. Leach, B.E.M. (Pp. 251+vii; illustrated. 35s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

BRITISH MEDICAL JOURNAL
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SURVIVAL OF BONE-MARROW GRAFTS

The danger of destruction of bone marrow from exposure to short-wave radiations and high-energy atomic particles, whether in warfare or by accident, has stimulated much work with the aim of developing an effective therapy. Animal experiments, apparently initiated by P. E. Rekers,[1] and to which a very large contribution has been made by the Medical Research Council Unit at Harwell under Dr. J. F. Loutit, have shown that, when the haemopoietic tissue of an animal is destroyed by irradiation, it can be replaced by injecting intravenously a suspension of marrow cells from another animal. The survival and proliferation of such grafts is possible only because some of the injected cells colonize the vacant spaces in the bone marrow and because the body, as a result of the irradiation, fails to show its normal response of destroying foreign tissues by the elaboration of antibodies to them. So far can this acquired tolerance go that mice will tolerate the haemopoietic tissues of rats. In the end the host animal sometimes dies, not because it destroys the engrafted tissues which are now essential to its existence, but because cells derived from engrafted lymphoblasts form antibodies which are lethal to the tissues of the host. This condition is known as homograft disease or runt disease.

When it was found that the haemopoietic tissues of an animal could be destroyed completely and replaced by a graft, the possibility was envisaged of curing in this manner malignant diseases of the haemopoietic system such as the leukaemias, as well as other diseases characterized by generalized and radiosensitive malignant growths. A few attempts have now been made on these lines to treat radiation injuries and malignant diseases in man. In some cases cytotoxic drugs such as the nitrogen mustards have been used instead of, or in addition to, irradiation, to destroy malignant cells. When radiation injury has occurred accidentally, it is necessary to use the marrow of a donor, who is virtually certain to differ antigenically from the recipient, unless an identical twin is available. But when deliberate irradiation or chemotherapy is to be carried out there may be a choice between using such a donor and removing before treatment some of the patient's own marrow, which will be injected into him later. This avoids the serious dangers of immunological incompatibility, but it is impossible to be certain, especially in leukaemia, that some of the cells so removed and re-infused are not themselves malignant.

When the patient's own marrow cells have been retransfused, there have been in a number of cases indications that they have become implanted, but the possibility of a purely humoral effect of the transfusion, acting on haemopoietic tissue surviving *in situ*, as suggested by Barnes and colleagues,[2] must in all cases be considered. In the case of autotransfusions, moreover, there appears to be no way of distinguishing between the prolonged survival of implanted cells and the recovery of cells which remained in the body all the time. Only in the case of marrow from a donor is it possible to demonstrate prolonged survival when this occurs. The most impressive examples of implantation of "foreign" marrow cells in man have been the three examples[3–5] now known of exchange of such cells between non-identical twins before birth. Here the mutual immunological tolerance is to be attributed to the foetal character of both the recipient's tissues and the implanted cells at the time of implantation.

The transfusion of marrow-cells after radiation injury has been reported in a series of papers[6–8] on the cases of six laboratory workers in Belgrade who received heavy dosages of neutrons and γ-rays as the result of an accident in the operation of an atomic reactor. It was judged that five had received dosages which would, without treatment, have been lethal, or in one case "supralethal," while the sixth was thought to have received a "sublethal" dose. All six were immediately flown to Paris, where they were treated at the Hôpital Curie. The patients received transfusions of blood, packed red cells, concentrated platelets, and γ-globulin, as well as antibiotics, and

[1] Rekers, P. E., *Transplantation of Bone Marrow into Dogs that have received Total Body Simple Dose Irradiation*, University of Rochester Atomic Energy Project U.R. 11, 1948.
[2] Barnes, D. W. H., Micklem, H. S., and Loutit, J. F., *Brit. med. J.*, 1960, 1, 643.
[3] Dunsford, I., Bowley, C. C., Hutchison, A. M., Thompson, J. S., Sanger R., and Race, R. R., ibid., 1953, 2, 81.
[4] Booth, P. B., *et al.*, ibid., 1957, 1, 1456.
[5] Nicholas, J. W., Jenkins, W. J., and Marsh, W. L., ibid., 1957, 1, 1458.
[6] Jammet, H., *et al.*, *Rev. franc. Et. clin. biol.*, 1959, 4, 210.
[7] Mathé, G., *et al.*, ibid., 1959, 4, 226.
[8] Salmon, C., ibid., 1959, 4, 239.
[9] Thomas, E. D., Lochte, H. L., and Ferrebee, J. W., *Blood*, 1959, 14, 1.
[10] Humble, J. G., and Newton, K. A., *Lancet*, 1958, 1, 142.
[11] Kretchmer, *Blood*, 1958, 13, 297.
[12] Bridges, J. B., *et al.*, *Lancet*, 1960, 1, 629.
[13] Beilby, J. O. W., Cade, I. S., Jelliffe, A. M., Parkin, D. M., and Stewart, J. W., *Brit. med. J.*, 1960, 1, 96.
[14] Mathé, G., and Bernard, J., Seventh European Congress of Haematology, London, Abstracts, 1959, Abstract No. 278.
[15] Brucer, M. (compiled by), *The Acute Radiation Syndrome*, a medical report on the Y-12 accident, June 16, 1958. United States Atomic Energy Commission Report ORINS - 25, Washington.
[16] Kay, H. E. M., and Constandoulakis, M., *Brit. med. J.*, 1959, 1, 575.

their blood picture was followed closely. Fourteen days after the accident the severe depletion of red cells and almost complete absence of the other formed elements in the blood of the most severely affected case led to an attempt at the grafting of haemopoietic tissue by the transfusion of nucleated cells derived from the liver and spleen of a premature infant which had died soon after birth. The choice of foetal cells for transfusion was made in an attempt to avoid any immune reaction of the transfused tissue against the host tissues. However, no clinical improvement and no perceptible haematological change followed, and 13 days later, or 27 days after the accident, a transfusion of adult bone-marrow cells was given. The immediate haematological response was good, but the patient died on the 32nd day as a result of irradiation damage to the viscera.

At about the same time all the other patients except the one least affected were given transfusions of adult marrow cells. In every case, including that of the patient who died, the donors were chosen as having blood group phenotypes as close as possible to those of the recipients, but in each case at least one antigenic difference made differential agglutination studies possible. A female donor was chosen for the female patient. All improved rapidly and appear ultimately to have recovered more or less completely. The remaining patient recovered slowly without marrow transfusion.

In the four surviving patients who received marrow-cell transfusions the red cells derived from the transfused marrow were traced by means of differential blood counts. It is clear that in all four cases some of the transfused erythroblasts became established in the patient's marrow, the most definite evidence being that the total numbers of foreign red cells found to have entered the circulation in all cases exceeded the numbers of cells transfused. Thus true marrow grafts must have become established. Cells derived from these, after an initial rise, gradually fell in numbers, and had almost disappeared at the end of the time of observation, some twelve weeks after the marrow transfusion took place. At no time were foreign cells found to be in a majority in any patient. The rapid rise in the granulocyte and thrombocyte counts after the transfusion suggests that myeloblasts and megakaryocytes also established themselves in the patient's marrow, but no serological evidence of this could be obtained. Since no male patient was given marrow from a female donor it was not possible to use observations of sex chromatin for this purpose. The evidence thus indicates that in all four cases marrow grafts became established, assisted in the symptomatic recovery, and may have been life-saving, but after three months had almost if not completely ceased to function.

E. D. Thomas and colleagues[9] have described a series of attempts to treat leukaemia by whole-body irradiation followed by marrow transfusion. In one of their cases, where the donor was the patient's sister, 3% of donor cells could be detected after 61 days, but after 107 days numbers had fallen below the limit of detection, 0.02%. Nevertheless, the acquired tolerance of the recipient was such that a skin graft from the marrow donor, transplanted 99 days after irradiation and transfusion, was still persistent on the 203rd day. In the case of one other patient, who subsequently died, there was evidence that a marrow graft became established and temporarily functional. J. G. Humble and K. A. Newton,[10] in a preliminary account of the treatment by marrow-cell transfusion of five cases previously irradiated for leukaemia or carcinoma, briefly mention two of these where there were indications of the establishment of a graft. Kretchmer[11] mentions a case of leukaemia in which, several months after irradiation and marrow transfusion, "there was evidence that donor-type cells were still present." J. B. Bridges and colleagues[12] have reported the case of a woman with breast cancer, treated with cytotoxic drugs, who received foetal liver suspension for marrow failure and responded strikingly.

By far the longest record persistence of an artificial marrow graft in man is that described by J. O. W. Beilby and colleagues[13] in a recent number of this journal. The patient, a woman, was suffering from Hodgkin's disease, clinically typical and confirmed by biopsy. The disease was at first controlled by *x*-ray therapy, and subsequently treated with chlorambucil and metachlorambucil, two of the nitrogen mustards. In the course of this treatment she developed a severe degree of marrow hypoplasia, with extreme deficiency of all the formed elements of the peripheral blood. Her condition deteriorated despite blood transfusion, and finally she was given a transfusion of marrow cells from her sister, estimated to contain 1.1×10^9 nucleated cells. This was followed by an immediate improvement in her clinical condition and a steady improvement in the haematological state. Four months later, when all original cells from the blood and marrow transfusions must have disappeared, cells could still be detected having the three blood-group antigens D, E, and M possessed by the marrow donor, but not by the patient. These can have been derived only from a successful marrow graft. During the first three months after the marrow transfusion the proportion of donor cells was found to vary between

0 and 6%, but 6 months afterwards they had risen to 24%, and three months later to 40%. Though the D antigen is particularly effective in causing immunization, the recipient did not develop anti-D. She did not, however, tolerate a skin graft from the marrow donor. Nine months after the transfusion she was still clinically well.

A warning against undue optimism is given by a preliminary communication from G. Mathé and J. Bernard[14] on three cases treated by irradiation followed by transfusion of marrow cells from donors. In the two cases in which a graft appeared to have been established there was a later development of the characteristic signs of homograft disease. It was apparently largely for fear of this disease that none of the eight persons affected by a radiation accident in America on June 16, 1958,[15] were treated by marrow transfusion. They were all, however, less severely affected than the Belgrade cases, and all made an apparent recovery on conservative treatment.

Though all these cases form a somewhat heterogeneous collection, certain generalizations can be made. It has not yet proved possible in man, as it has in animals, to destroy completely and then replace any subject's haemopoietic tissue. It may indeed be that, as suggested by the case most severely affected by the Belgrade reactor accident, such a state of affairs is incompatible with survival, because of irreversible damage to other tissues. Nevertheless, the incomplete destruction (and partial replacement) which has occurred in human beings has been accompanied in two cases at least by the prolonged if not permanent arrest of a generalized malignant process. Thus further attempts at such therapy in carefully selected cases appear to be justified. The dangers of homograft disease, however, make it desirable that persistent attempts should be made to develop the use of foetal haemopoietic cells[16] for transfusion and, in suitable cases, the patient's own preserved cells.

It is certainly important, at the present stage, that in every case all possible measurements and observations should be made which might give guidance in subsequent attempts at similar treatment, and reports on all cases, whether successful or not, should be published. Even if the use of homografts from adult donors should ultimately have to be discontinued, immunological study after they or foetal homografts have been given is particularly important, for thus we can obtain information on the fate of grafts generally such as cannot be obtained from the observation of autografts.

Much more work is needed on the immunological properties of different normal tissues and malignant growths. For instance, since it is known that in general the antigens of the blood groups differ from those concerned with skin-graft incompatibility, and since the mechanisms of immune response are different, it is not surprising that grafts of skin and of haemopoietic tissues behave differently. But it is not clear why in one case a skin graft from a marrow donor has persisted though the marrow graft has disappeared, while in another the marrow but not the skin graft has survived. However, it is significant that in both cases the donor was a sister of the recipient, a circumstance which must have minimized the antigenic differences in both kinds of tissue. Until we know much more about the antigens involved it will continue to be advisable, where possible, to obtain marrow grafts from near relatives. It is important to know whether leucopoietic tissues survive in grafts, and for how long. So long as immunological tests are not available, it is worth considering whether female donors should be used for male recipients so as to make possible the observation of sex chromatin in the circulating leucocytes as an index of survival, as has been done in natural blood chimeras.

NASAL SPEECH

The acquisition of speech was probably the main evolutionary factor leading to man's pre-eminence in the animal kingdom, and even the most primitive known peoples have this gift. Yet, though speaking is a universal accomplishment of the human race, few people ever take the trouble to learn how to speak properly.

Speech is produced by organs primarily evolved for breathing and swallowing. Air is squeezed from the lungs through the larynx and is set in vibration by movements of the vocal cords. The noise thus produced is made into intelligible speech by what are known as the moulds of speech—namely, the pharynx, tongue, lips, palate, teeth, nasal cavities, and nasal accessory sinuses. Some of these organs give the voice resonance, while others are concerned with articulation. These two qualities cannot be completely separated, as both depend on muscular movements which alter the size of the pharyngeal, oral, and nasal cavities, as well as the tension of their walls. Speech is thus a complicated and exacting art, and it is really a matter of wonder that most of us speak as well as we do, for we acquire the art almost fortuitously by mimicry in childhood.

[1] Ellis, M., *J. Laryng.*, 1959, **73**, 99.
[2] Gibb, A. G., ibid., 1958, **72**, 433.

Not surprisingly, this process results in many functional speech defects.[1] Even in adults defects in resonance, articulation, and phrasing are not uncommon. But there are other defects due to organic lesions of the structures concerned in the production of speech. Among them is the condition known as rhinolalia, which is the name given to an unpleasant nasal quality in the voice. Some degree of nasality is normal in a good speaking voice, which owes part of its carrying power to this quality, particularly in the frequencies of 300 to 600. Nasality is usually produced in the nasal cavities, but it is sometimes produced in the pharynx, especially when acquired or imitative. For instance, the nasal twang of New England speech, the so-called Oxford drawl, and various other forms of drawling speech due to affected nasal accentuation all result from pharyngeal constriction.

The nasal cavities normally act as resonators. They lead off the main pharyngeal cavity by an opening between the soft palate and the posterior pharyngeal wall, and they communicate with the outside world by means of the anterior nares. Variations in nasal resonance depend on the relative size of these two openings. Defects in nasal resonance occur either when the nasopharyngeal aperture is too open, or when it is obstructed, conditions known respectively as rhinolalia aperta and rhinolalia clausa.

Closure of the nasopharyngeal aperture is normally achieved by contraction of the soft palate and particularly by contraction of the superior constrictor muscle, as described by the nineteenth-century German surgeon Passavant, and the ridge formed across the pharynx by the contracted superior constrictor muscle is known as Passavant's bar or ridge. In rhinolalia clausa the resonating capacity of the nasal cavities remains unused, because they are shut off from the main speech tract. Owing to this lack of resonance, the condition is sometimes called hyporhinophonia. In rhinolalia aperta the reverse condition holds, and the nasal cavities open only too well into the main speech tract, resulting in an excessive degree of nasal resonance, or hyperrhinophonia. This occurs in palatal defects such as congenital clefts, erosion by disease, or immobility from trauma or interrupted innervation. It also occurs when the palate is too short and does not meet the posterior pharyngeal wall when contracted.

Speech therapists have long been aware of the danger of rhinolalia developing after adenoidectomy. Sometimes a large pad of adenoid tissue may prevent the soft palate from meeting the posterior pharyngeal wall when both contract, leading to a functional habit, and to a secondary shortening of the palate by adaptation. In other cases palatal bruising at operation may cause disuse through pain, again resulting in an adaptational shortening. In rare cases palatal scarring and contracture may follow the operation. A short soft palate, however, is sometimes congenital. A. G. Gibb[2] has recently reviewed some cases of post-adenoidectomy rhinolalia, and believes that congenital shortening together with diminished post-operative movement was the chief cause. He says that it is a little-known, or little-considered, complication of the operation. This may be true, but it is fair to add that permanent rhinolalia arising in this way is also rare. Most patients with post-operative nasal voice recover in a few weeks or months, especially if the child is encouraged to attack a normal diet within two or three days of operation, and is made to do breathing exercises if any nasality is noticed. If the nasality persists for longer than three or four weeks, the aid of a speech therapist should be enlisted. There may be less risk of developing rhinolalia aperta if the operation is performed when the child is young, for then the powers of repair are greater. The possibility of this unusual complication can scarcely be held a contra-indication to an operation considered necessary for important reasons.

When the palate is congenitally short, a good voice free of hypernasality is usually acquired spontaneously, and in any ear, nose, and throat out-patient clinic the condition will be noticed as an incidental finding in patients who have come for advice on other matters. The efficiency of the action of the superior constrictor muscle is an important factor, and in addition there seems to be an unknown, idiosyncratic factor whereby one person may succeed in achieving what another with a virtually identical anatomical structure fails to achieve. Nevertheless, some patients with congenitally short palates fail to acquire a good speaking voice, and narrowing the nasopharyngeal space by the implantation of cartilage under the superior constrictor muscle in the prevertebral region has been performed, with encouraging results. This should probably be a last resort when all other means of functional training have failed.

MAGNESIUM DEFICIENCY

The concentrations of magnesium in the intracellular and extracellular compartments of the body fluids are about 40 mEq per litre and 2 mEq per litre respectively. Though tetany due to dietary magnesium deficiency ("grass staggers") occurs in dairy cows,[1] little attention has been paid to the possible role of changes in the general magnesium balance or of abnormal fluxes of magnesium ions between the intracellular and extracellular fluids in the aetiology of human disease.

Magnesium depletion in man (as judged by the occurrence of hypomagnesaemia) results in tetany which is indistinguishable clinically from that due to hypocalcaemia. It may be associated with choreoathetosis, tremulousness, myoclonus, muscle fibrillation, generalized epileptiform convulsions, and hyperreactivity to mechanical or auditory stimulation.[2 3] Episodes of delirium and mental confusion have been attributed to magnesium depletion, though there appears to be no direct correlation between the patient's level of consciousness and the level of magnesium in the serum. A. D. Hirschfelder and V. G. Haury were among the first to suggest that hypomagnesaemia might be associated with increased neuromuscular excitability,[4] and E. B. Fink and colleagues suggested that magnesium depletion was responsible for some of the clinical manifestations of delirium tremens.[5] B. L. Vallee and his colleagues[2] have demonstrated that hypomagnesaemic tetany may occur in chronic alcoholics, but that the restoration and maintenance of a normal level of magnesium in the serum, with abolition of tetany, does not prevent the occurrence of delirium tremens. These workers found that the normal serum-magnesium level varied between 1.75 and 2.49 mEq/litre; the distribution of values about the mean value of 2.0 mEq/litre was Gaussian with a standard deviation of 0.16 mEq/litre (90 observations), and tetany occurred when the serum-magnesium concentration was in the range 0.60 to 1.33 mEq/litre.

Magnesium depletion may be expected to become of clinical importance when a low intake of magnesium is associated with abnormal loss of gastro-intestinal secretion, as in the chronic alcoholic patient with severe emesis previously referred to.[2] Similar circumstances prevail when continuous intestinal aspiration is combined with the infusion of magnesium-free fluids. Patients with intestinal fistulae, intractable diarrhoea, diabetic ketosis, and those in the diuretic-phase of the recovery from acute renal insufficiency may become depleted of magnesium. J. R. Squire and his colleagues[6] have recently reported a case in which a woman of 39 developed a malabsorption syndrome after resection of a large loop of twisted small intestine. The magnesium levels in serum and urine were very low, and the oral administration of magnesium hydroxide was associated with immediate improvement and appears to have been responsible for the ultimate favourable outcome. Hypomagnesaemia has also been reported in association with the prolonged use of mercurial diuretics and kation-exchange resins simultaneously.[7] Magnesium depletion can be corrected by oral administration or by intramuscular injections, the total amount given being controlled by the serum-magnesium level.[2 6]

The development of the flame spectrophotometer,[8 9] which permits rapid and precise measurement of the serum-magnesium level, should stimulate the study of patients who are exposed to the risk of magnesium depletion. It may be that minor degrees of the condition will be recognized and that their early correction will improve the prognosis of the underlying disease.

[1] Underwood, E. J., *Ann. Rev. Biochem.*, 1959, **28**, 499.
[2] Vallee, B. L., Wacker, W. E. C., and Ulmer, D. D., *New Engl. J. Med.*, 1960, **262**, 155.
[3] Randall, R. E., Rossmeisl, E. C., and Bleifer, K. H., *Ann. Intern. Med.*, 1959, **50**, 257.
[4] Hirschfelder, A. D., and Haury, V. G., *J. Amer. med. Ass.*, 1934, **102**, 1138.
[5] Fink, E. B., Stutzman, F. L., Anderson, A. R., Konig, T., and Fraser, R., *J. Lab. clin. Med.*, 1954, **43**, 169.
[6] Fletcher, R. F., Henley, A. A., Sammons, H. G., and Squire, J. R., *Lancet*, 1960, **1**, 522.
[7] Martin, H. E., Mehl, J., and Wertman, M., *Med. Clin. N. Amer.*, 1952, **36**, 1157.
[8] Vallee, B. L., and Mangoshes, M., *Analyt. Chem.*, 1956, **28**, 175.
[9] MacIntyre, I., and Davidsson, E., *Biochem. J.*, 1958, **70**, 456.

TEACHING OF SOCIAL MEDICINE

Following the example of London and Cambridge, the University of Oxford no longer includes public health as a final examination subject. It is therefore timely that the British Medical Students' Association's report on the teaching of social medicine,[1] the result of a resolution passed at its 17th Annual General Meeting in 1958, should just have been published. Though the report is a combined effort, the person on whom most of the labour fell was R. N. M. MacSween, who was a final-year medical student at the time the work was done. He collected his data by sending questionaries to students who were members of the association in schools throughout the country; they obtained factual information about the time devoted to and methods of teaching from their medical school office, and in addition canvassed student opinion about the adequacy and effectiveness of the course. In the published report fact and opinion are clearly differentiated; the former is listed under the name of the school concerned, the latter is couched in general terms and "in no way directed at the individual schools." It is unfortunate that the data are incomplete; some schools are omitted because their B.M.S.A. representative failed to return the questionary before the report went to press; others are not affiliated, and though the deans gave particulars of teaching arrangements the views of the student body on these were not obtained. In all, 17 clinical schools co-operated to a greater or less extent. Nevertheless the report, which was accepted unanimously at a national meeting of the B.M.S.A. in November, 1959, is informative and of considerable interest.

The report is very strongly in favour of a full course in social medicine, and, although "in some of its aspects [it] could well be integrated with some other of the subjects in the clinical curriculum, it ought still to have such a position of importance . . . as to merit its being taught as a separate entity." The subjects to be included are: (1) epidemiology; (2) medical sociology; and (3) the organization and working of the National Health Service; "In addition more emphasis should be placed on the social aspect of clinical cases in the wards." The value of visits to factories, special clinics, and patients' homes is stressed; the latter being considered more instructive when made with the general practitioner, almoner, or health visitor. On the contentious subject of examinations, the report suggests that social medicine as such should not be included as a subject in the final examination, but that a combined

[1] *Report on the Teaching of Social Medicine in British Medical Schools*, edited by R. N. M. MacSween, 1960. B.M.S.A., publication.

examination in social medicine and infectious diseases would be suitable.

Though the report is obviously not representative of all student opinion in the United Kingdom, it should not be lightly dismissed on that account, for the curriculum is doubtless a frequent topic of conversation among students whether or not they are actively engaged in the affairs of the B.M.S.A., so that the opinions of those who played a part in the study were presumably coloured to some extent by the remainder. Furthermore, the report gives the impression that there was a wide measure of agreement between the schools, and this is unlikely to be the result of collusion. It is to be hoped that the deans and councils of medical schools will consider it when they are discussing how best to deal with the teaching of social medicine. At the same time they could also usefully consider something which students in Britain are naturally not equipped to do—namely, American experiments in the teaching of social medicine as a part of other branches of medicine.

DRUG-INDUCED MALABSORPTION OF FOOD

Malabsorption of food material from the intestine is usually seen as a consequence of disease. Recently another side of the question has come up. J. A. Nissim,[1] while studying in mice the pharmacological properties of a synthetic bactericidal substance, trimethylhexadecylammonium stearate, noticed that the animals lost weight without reducing their consumption of food except just before death. Those animals receiving 0.4–0.5% of the drug in their diet died in less than three weeks, and showed haemorrhagic changes extending from the pyloric portion of the stomach to the ileum, with damage to the epithelial lining of the intestinal villi. Animals receiving smaller amounts of the drug survived for longer periods and haemorrhages were absent; some cases showed hypertrophy and hyperplasia of the duodenum and jejunum. These mucosal changes were found irrespective of the route by which the drug was administered, though it was more toxic when given subcutaneously or intraperitoneally than orally. Animals allowed to recover, by stopping the drug after they had lost ⅓–¼ of their body weight, were restored to normal weight when allowed an unrestricted diet. Three months after the end of the experiment these animals were indistinguishable from those in the control group.

A healthy adult male volunteer who was given the drug intermittently lost 20 lb. (9 kg.) in weight. This was reversible and was associated with some increase in bulk and softness of the stools. As Nissim points out, such a substance may be useful as a research tool in the study of intestinal absorption and therapeutically in the control of obesity.

Food absorption entails the passage of the breakdown products after digestion through the intestinal mucosal cell into the blood or lymph. Thus, digestible carbohydrates are first converted to monosaccharides. But absorption is not only a matter of simple diffusion: if it were, pentoses with small molecules would be absorbed more rapidly than hexoses, whereas the reverse normally occurs[2] There is much evidence in both man and animals that absorption is selective by an active process[3 4] To explain this, a mechanism involving phosphorylation of sugar has been postulated.[5 6] The effective concentration of free sugar within the mucosal cell would fall as fast as it enters, resulting in a steep diffusion gradient and rapid absorption. But other factors are also at work: thus absorption is hindered in animals by starvation, adrenalectomy, and vitamin deficiency and aided by administration of thyroid. Proteins are probably absorbed largely as amino-acids, and this, too, seems to be an active process.[4 7–9] Complex interrelations exist, as it has been shown that some amino-acids compete with each other for active transport[10]

There are two main theories of fat absorption. The lipolytic theory postulates that fat is hydrolysed completely in the intestine to glycerol and fatty acids which, with the aid of bile salts, are absorbed into the cells of the intestinal mucosa. Here resynthesis to triglycerides occurs, phosphorylation being an intermediate stage.[11] The other theory postulates the partial hydrolysis of triglycerides to lower glycerides and fatty acids.[12] These, with the unchanged triglycerides and bile salts, form an emulsion with a particle size of less than 0.5μ, which is absorbed into the mucosal cells, where some phospholipid is formed. Eventually particulate triglycerides are reformed and pass via the chyle into the systemic circulation. The short-chain fatty acids resulting from hydrolysis, being water-soluble, are thought to pass mainly into the portal blood after absorption.

Thus, although much of the evidence on absorption of food is obtained from animal experiments and some *in vitro*, it seems likely that in man it is also an active process. Disruption of the process, perhaps through interference with enzyme activity, would result in diminished absorption of food and consequent loss of weight. If a drug could be found which accomplished this without causing irreversible damage or toxic reactions, and without seriously reducing the absorption of other essential nutrients such as vitamins, electrolytes, water, and haematinic substances, a new treatment for obesity—one of the most difficult conditions to treat effectively—might be possible.

[1] Nissim, J. A., *Nature* (*Lond.*), 1960, **185**, 222.
[2] Auchinachie, D. W., MacLeod, J. J. R., and Magee, H. E., *J. Physiol.* (*Lond.*), 1930, **69**, 185.
[3] Groen, J., *J. clin. Invest.*, 1937, **16**, 245.
[4] Wilson, T. H., and Wiseman, G., *J. Physiol.* (*Lond.*), 1954, **123**, 116.
[5] Verzár, F., and McDougall, E. J., *Absorption from the Intestine*, 1936, p. 130, London.
[6] Jervis, E. L., Sheff, M. F., and Smyth, D. H., *J. Physiol.* (*Lond.*), 1956, **131**, 16P.
[7] Höber, R., and Höber, J., *J. cell. comp. Physiol.*, 1937, **10**, 401.
[8] Gibson, Q. H., and Wiseman, G., *Biochem. J.*, 1951, **48**, 426.
[9] Jervis, E. L., and Smyth, D. H., *J. Physiol.* (*Lond.*), 1959, **149**, 433.
[10] Wiseman, G., ibid., 1955, **127**, 414.
[11] Verzár, F., and McDougall, E. J., *Absorption from the Intestine*, 1936, p. 210, London.
[12] Frazer, A. C., *Lectures on the Scientific Basis of Medicine*, Volume IV, 1956, p. 311, London.

Drug Treatment of Disease

IRON PREPARATIONS FOR ANAEMIA

BY

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More than twenty years ago ferrous sulphate became established as a highly satisfactory and economical preparation for the treatment of iron-deficiency anaemia. Studies such as those of Witts (1936) and Davidson and Fullerton (1938) showed it to be at least as effective as any of the other iron compounds available at that time, including ferrous lactate, ferrous chloride, ferrous carbonate, iron and ammonium citrate, and colloidal iron, while it was cheaper and more convenient to dispense than any other compound.

In more recent years, however, a series of organic iron preparations such as ferrous gluconate, succinate, and fumarate and a range of chelated iron compounds have been introduced, to the accompaniment of extensive advertising campaigns, as supposedly more effective and less toxic alternatives to ferrous sulphate. In the first part of this article I propose to examine how these claims have survived the clinical trials designed to confirm or refute them. I shall then deal briefly with the question of comparative costs of oral preparations, and finally describe the compounds available for parenteral use.

EFFICACY AND TOXICITY

O'Sullivan *et al.* (1955) carried out one of the first reliable trials on the comparative value of ferrous sulphate, gluconate, and succinate. Tablets were given in doses arranged to provide equal amounts of elemental iron, 210 mg. daily, to groups of comparable patients, and the response was assessed with regard to rise of haemoglobin and the incidence of side-effects. There was little difference in efficacy between the three compounds, each producing an average daily haemoglobin rise between 1.1 and 1.25%. Gastro-intestinal symptoms of intolerance occurred in 3 out of 23 patients taking ferrous sulphate, in 1 out of 25 taking ferrous gluconate, and in 1 out of 25 taking ferrous succinate.

A survey of many papers dealing with the incidence of gastro-intestinal intolerance including nausea, vomiting, constipation, or diarrhoea during oral iron therapy strongly suggests that intolerance results chiefly from giving unnecessarily high doses, irrespective of the compound employed, or from psychological factors.

So far as dosage is concerned, quantities of elemental iron in excess of 300 mg. daily appear to have been given in most series of cases in which the figures for intolerance were high, and such high doses are certainly not necessary. Brumfitt (1959) found satisfactory and similar responses to either ferrous sulphate or ferrous gluconate in daily doses containing 149 mg. of elemental iron, roughly equivalent to two standard pills of ferrous sulphate or four of ferrous gluconate. None of the 30 patients included in this comparative trial developed symptoms of intolerance to either drug, and there was no intolerance among a further 50 patients treated with ferrous sulphate in similar dosage.

Psychological Intolerance

The psychological aspects of intolerance were first emphasized by Girdwood (1952). He found that 14 out of 16 patients who had developed gastro-intestinal symptoms while taking green ferrous sulphate tablets no longer did so when the same quantity of ferrous sulphate was taken in white pills. The possibility that suggestible subjects might tend to develop symptoms of intolerance when taking the familiar green ferrous sulphate tablets commonly issued at antenatal clinics, because they think side-effects are likely to occur rather than because the iron compound genuinely induces them, gains further support from figures of the incidence of intolerance in pregnant women given pills of differing appearance. Intolerance rates between 15 and 60% have commonly been encountered in pregnant women given standard green tablets in a dosage of 200 to 360 mg. of elemental iron daily, the higher rates of intolerance generally being associated with higher levels of dosage (Benstead and Theobald, 1952; Gatenby and Lillie, 1955; Talaga, 1955), whereas Edgar and Rice (1956) found intolerance in less than 5% of a large number of patients taking ferrous sulphate made up in white tablets with a daily intake of 200 mg. of iron.

A careful study of gastro-intestinal intolerance to oral iron compounds was made by Kerr and Davidson (1958a). They administered ferrous sulphate, ferrous gluconate, ferrous succinate, and ferrous calcium citrate in daily doses containing 105 mg. of elemental iron, and "known" and "unknown" control pills containing lactose to 93 healthy young women in a trial conducted so far as possible on the "double-blind" principle—that is, neither patient nor doctor was aware which of the preparations had been given to any individual, except in the case of the "known" control pills. None of the four iron compounds was found to induce toxic effects more frequently than did the "unknown" control pills containing lactose; for all these preparations the incidence of gastro-intestinal symptoms was between 15 and 20%. The "known" control pills produced virtually no toxic effects. The authors concluded that intolerance to these iron compounds, in the dosage given, was mainly psychological in origin.

Chelated Compounds

Fewer comparative trials have been conducted with the more recently introduced chelated iron compounds. These compounds are generally ring structures in which metallic iron is bound in a stable manner in an organic molecule. Herridge (1958) treated 10 patients with a form of "sytron" elixir, containing the ferric sodium salt of ethylenediamine tetra-acetic acid, and compared the response of their iron-deficiency anaemia with that of a further 20 patients treated with ferrous gluconate or succinate. Those receiving the chelate showed a significantly greater rise of haemoglobin, but the dosage of chelate in terms of elemental iron was between two

and three times that of the other salts. Perhaps for the same reason gastro-intestinal intolerance was greater in the patients taking chelate. Jennison (1958) found ferrous aminoacetosulphate ("plesmet") more effective and less toxic than ferrous gluconate when given to pregnant women with iron deficiency, but studies with other chelates (Seeberg *et al.*, 1954; Will and Vilter, 1954; Franklin *et al.*, 1958) appear to show that this type of compound is in general no better absorbed or tolerated than similar doses of ferrous sulphate. There therefore seems to be no great advantage to be gained from the use of chelates in the treatment of most patients with iron deficiency.

Post-gastrectomy Anaemias

In iron-deficiency anaemia following partial gastrectomy, on the other hand, there is some tentative evidence that iron chelates may have a special therapeutic place, since Hobbs and Discombe (1959) found a constant and rapid response to ferrous glycine sulphate, a chelated form of iron, whereas the response to ferrous sulphate proved erratic and unsatisfactory.

We may conclude from these studies that when minimal effective doses of ferrous sulphate are used—namely, 2 to 3 standard tablets daily, equivalent to 120 to 180 mg. elemental iron—the risk of intolerance is small. It can be further reduced by carefully avoiding any suggestion that gastro-intestinal disturbance may develop. Organic compounds such as ferrous gluconate and succinate, the equally effective ferrous fumarate, and the various chelated compounds appear to have no significant advantage over ferrous sulphate in terms of efficiency of action or incidence of side-effects when ferrous sulphate is given in the manner described. This statement applies to the great majority of cases of iron-deficiency anaemia, though it remains possible that organic salts or chelates may have a special advantage in the treatment of certain post-gastrectomy anaemias.

Dangers to Children

All oral iron compounds should be kept well out of the way of children, since they may readily be mistaken for sweets and consumed in large quantities. Relatively small overdoses of these compounds, and especially ferrous sulphate, may be highly dangerous to children.

COMPARATIVE COSTS

Since all the forms of iron hitherto discussed appear generally comparable in therapeutic efficiency and in toxicity when given in equivalent dosage with regard to content of elemental iron, their relative costs should clearly influence prescribing. Davidson and Richmond (1958) have examined this problem in detail, using figures from official sources and dealing with prescriptions dispensed throughout Scotland during May, 1957. They found that between 3 and 3½ million iron tablets were being dispensed each month in family practice, some 23% of them being ferrous sulphate, 50% ferrous gluconate, and 27% ferrous succinate. In hospitals about 10 million tablets were dispensed annually, about 46% being ferrous sulphate, 46% ferrous gluconate, and 8% ferrous succinate.

Now the cost of organic iron salts is much higher than that of ferrous sulphate, varying from five to 10 times the price for an equivalent iron content in the commonly used preparations and being considerably higher, sometimes very much higher, for chelated compounds and preparations with added vitamins. If ferrous sulphate were always preferentially prescribed, Davidson and Richmond calculated that there would be a saving of about £40,000 per annum in Scotland alone. The pattern of prescribing may differ in England and Wales from that in Scotland, but if it is roughly the same the comparable saving to be achieved by the use of ferrous sulphate would be about £360,000 per annum. Moreover, since ferrous sulphate is customarily given in unnecessarily large doses, the use of minimal effective doses would further reduce the drug bill.

Vitamins

There is no real justification for giving iron preparations with added vitamins in the treatment of uncomplicated iron deficiency. The only vitamin known to facilitate absorption of iron is ascorbic acid, but with therapeutic doses of iron the addition of ascorbic acid does not appear to increase the efficiency of action and may reasonably be regarded as a needless expense (Kerr and Davidson, 1958b). Vitamins of the B group, added to several proprietary iron preparations, play no part in iron absorption, but greatly increase the cost.

PARENTERAL IRON

Two preparations have come into general clinical use for the parenteral administration of iron to patients who are undoubtedly intolerant of oral compounds, fail to absorb iron given by mouth, need rapid reconstitution of iron reserves, or have some gastro-intestinal disease liable to exacerbation if iron is given orally.

The first, saccharated iron oxide, is given intravenously, usually in doses of 5 ml., containing 100 mg. of iron, to a total calculated from the degree of anaemia, but commonly ranging from 1,000 mg. to 3,500 mg. in an adult. Care must be taken to give a clean intravenous injection, since the material is very irritant if deposited in the subcutaneous tissues. Reactions have proved a troublesome complication, though something can be done to reduce their incidence by the use of a small trial dose (25 mg.) before the course is undertaken, patients showing any sign of reaction to the initial dose being treated by some other means.

The chief features of the reactions to intravenous iron include cardiovascular symptoms, with fall of blood-pressure, tachycardia, and sometimes loss of consciousness, dyspnoea, cyanosis, vomiting, diarrhoea, and abdominal pain, and high pyrexia with rigors. They are of rapid onset, usually starting during the injection or within half an hour of its completion. Ross (1957) reported the incidence of toxic reaction in 802 anaemic patients treated with a standard preparation of intravenous saccharated iron oxide—"ferrivenin." With 100-mg. doses the overall incidence was 7.5%, and with 500-mg. doses the incidence rose sharply to 43%. Even with careful selection of patients, excluding those with chronic heart or lung disease who seem especially liable to respiratory reactions, and the use of no more than 100-mg. doses, the incidence of reactions is likely to remain about 5%.

The second iron compound for parenteral administration is an iron-dextran complex, "imferon," given by intramuscular injection. While it has been shown to be relatively free from immediate toxic effects, recent animal experiments have demonstrated a marked carcinogenic hazard of iron-dextran in rats and mice (Richmond, 1959; Haddow and Horning, 1960). I am not aware of any reports of local tumour formation

after imferon injections in man, despite very extensive use over the past five years, and it may be that the hazard does not apply to all species. Nevertheless, until the risks to man have been elucidated it would seem wise to discontinue the use of iron-dextran in medical practice (*Brit. med. J.*, 1960).

CONCLUSIONS

Ferrous sulphate in relatively small doses (2 to 3 tablets of 0.2 g. daily, providing 120 to 180 mg. elemental iron) is the most economical form of oral iron for general use. It is not significantly inferior to more expensive organic salts and chelates with regard to efficacy or gastro-intestinal toxicity when given in the proper dosage, and it is much cheaper.

Alternative oral preparations may reasonably be tried in the small proportion of patients who develop intolerance even to small doses of ferrous sulphate, though such patients may often react similarly to other compounds. For these intolerant patients, and for some others who fail to respond to oral iron or for other reasons require parenteral administration, intravenous saccharated iron oxide may be given, a careful watch being maintained for sensitivity reactions. Parenteral compounds are, of course, much more expensive than equivalent doses of oral iron, but in practice the high utilization of the iron reduces the difference in cost, and, since iron should not be given parenterally in preference to orally unless a specific indication exists, economic considerations are not of importance here.

REFERENCES

Benstead, N., and Theobald, G. W. (1952). *Brit. med. J.*, **1**, 407.
Brit. med. J., 1960, **1**, 788.
Brumfitt, W. (1959). Ibid., **2**, 473.
Cope, E., Gillhespy, R. O., and Richardson, R. W. (1956). Ibid., **2**, 638.
Davidson, L. S. P., and Fullerton, H. W. (1938). *Edinb. med. J.*, **45**, 193.
Davidson, S., and Richmond, J. (1958). *Lancet*, **2**, 570.
Edgar, W., and Rice, H. M. (1956). Ibid., **1**, 599.
Franklin, M., and Rohse, W. G., de la Huerga, J., and Kemp, C. R. (1958). *J. Amer. med. Ass.*, **166**, 1685.
Gatenby, P. B. B., and Lillie, E. W. (1955). *Lancet*, **1**, 740.
Girdwood, R. H. (1952). *Brit. med. J.*, **1**, 599.
Haddow, A., and Horning, E. S. (1960). *J. nat. Cancer Inst.*, **24**, 109.
Herridge, C. F. (1958). *Brit. med. J.*, **2**, 140.
Hobbs, J. R., and Discombe, G. (1959). Communication to 7th European Congress of Haematology, London, September, 1959 (to be published).
Jennison, R. F. (1958). *Brit. med. J.*, **2**, 567.
Kerr, D. N. S., and Davidson, S. (1958). *Lancet*, **2**, 489.
—— —— (1958). Ibid., **2**, 483.
O'Sullivan, D. J., Higgins, P. G., and Wilkinson, J. F. (1955). Ibid., **2**, 482.
Richmond, H. G. (1959). *Brit. med. J.*, **1**, 947.
Ross, I. P. (1957). *Lancet*, **2**, 77.
Seeberg, V. P., Hidalgo, J., and Wilken, W. (1954). *Science*, **119**, 608.
Talaga, E. S. (1955). *Obstet. and Gynec.*, **5**, 201.
Will, J. J., and Vilter, R. W. (1954). *J. Lab. clin. Med.*, **44**, 499.
Witts, L. J. (1936). *Lancet*, **1**, 1.

The booklet, *Home Guide for the Diabetic: Diet Instruction, Recipes and Other Guidance* (Iliffe and Sons, Ltd., Dorset House, Stamford Street, London, S.E.1, price 3s., by post 3s. 3d.), is based on the handbook issued to patients of the Leicester Royal Infirmary Diabetic Clinic. General guidance is given on such subjects as the method of giving insulin injections, hygiene for the diabetic, social-service arrangements, and general principles of nutrition. There are further sections on alternative food values, a special list of foods with low caloric value, recipes, weight-reducing diets, and a list of proprietary names of medical supplies.

MEDICAL RESPONSIBILITY IN ADOPTION

BY

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Psychiatrist to the Children's Society

The number of official adoptions in England and Wales is about 13,000 a year. Most of these entail a medical examination for purposes dissimilar in several respects from other types of medical examination. With the coming into force of a new Adoption Act it seems timely to consider what part the doctor plays in ensuring that adoption is practised wisely and with due regard to the well-being of the adopted children and society.

A doctor may be asked to examine and report on the health of a child proposed for adoption, or of the persons who propose to adopt. The request to do so will come from either the would-be adopters, the adoption agency (local authority or registered adoption society), or the mother who wishes her child to be accepted by an adoption agency for adoption.

The point at which the doctor will be approached is as soon as the question of getting a particular child adopted has been mooted, or when particular applicants have decided that they wish to adopt a particular child. He will be approached to examine the prospective adopters (*a*) when they make a general application to an adoption agency without specifying a particular child, or (*b*) when adopters are about to apply to a court for permission to adopt a particular child.

The doctor's report on the health of the infant has to be detailed and comprehensive, as required by the Regulations. His report on the health of the would-be adopters for the court will be summary; to meet the minimal requirements of the Act he need only state that the applicant whom he has examined "is physically, mentally, and emotionally suitable to adopt a child." Most of the adoption agencies, however, will ask for much more than this, and their forms are correspondingly more detailed—rather on the lines of a health insurance report. They pay particular attention to the applicants' emotional stability and medical reasons for not having children of their own instead of adopting. Medical reports on adopters are not required, however, when the child's natural parent (usually the mother of an illegitimate child) wishes to adopt him or when he is past compulsory school age.

As some of these requirements, especially those regarding a medical examination of the adopters, are new since the passing of the Adoption Act, 1958, it is likely that difficult questions of procedure and clinical appraisal will occasionally arise for doctors asked to assist in an adoption.

Reports on Infants

The examining doctor is not asked to give his opinion that the child is or is not suitable for adoption when he fills up the certificate for the court hearing; he is asked only to say, first, that he has informed the would-be adopters of his findings on mental and physical examination, and, secondly, that the child is or is not

normal. The last can be a difficult task. Few doctors would like to assess a child's mental normality when it is only a few weeks old. Unless a defect is gross, it is impossible to detect when the infant is very young; but doctors are often asked to examine an infant for adoption purposes within the first two months, since as soon as the infant is six weeks old its mother can consent to its being adopted, and three months later the adoption can be made legal and final. Some doctors believe that the examination should be carried out in all cases by a consultant paediatrician, but the Act does not require this.

The laboratory tests now needed to ensure that certain specific or hereditary disorders are not overlooked make considerable demands on the doctor. Among them is a serological test for syphilis, to be carried out six weeks or later after birth. There has been some comment about the practical difficulties encountered in getting this test done on a very young infant. An adoption society sometimes wants to place a child before it is 6 weeks old in the care of a couple proposing to adopt, the mother having given provisional consent. They may do so if the medical examination, apart from the serological test, is satisfactory; the serological test can in such a case be postponed until the child has reached the stipulated age. The responsibility for seeing to this rests with the adoption society.

The doctor's problem of getting blood from a very small infant is met by the technique described in the *Lancet* (1959): "Immerse the child's foot in hot water for a few minutes. Dry and apply a light tourniquet round the lower leg. Sterilize the skin of the fleshy part of the heel with spirit. After a few minutes stab the heel with a Hagedorn needle or make a small snick through the skin of the heel with a sterile safety-razor blade. The blood flows freely and can be collected in a test-tube; 2 ml. of whole blood is sufficient. The clean cut made by the blade is practically painless; bleeding soon stops when the tourniquet is removed, and healing is prompt."

The urine has to be tested for phenylpyruvic acid as well as for sugar and albumin. For this a fresh specimen is needed when the child is at least three weeks old. To get a specimen the doctor has to rely on the co-operation of parent or nurse. Simple techniques for this and the possibility of using the freshly wet napkin need to be further explored. Gibbs and Woolf (1959) found, after an extensive investigation of tests for phenylketonuria, that the "phenistix" strips put up by Ames & Co. provide a quick, easy, and reliable method. They suggest that routine testing may be carried out as early as 3 weeks but that a retest should be made at 2 months for complete safety.

These problems are small, however, in comparison with the difficulties of judging whether a newborn infant is and will be mentally normal. Paediatricians with special experience in this field feel able to express such an opinion only after the baby is 3 months old and even then with caution; nor can any but gross defects be detected with any confidence during the first year of life. It is therefore no easy matter for the doctor who has to examine the infant to explain to adopters the significance of what he has found, as the regulations require.

Explaining the Significance of the Findings to the Adopters

Any physical abnormality in the child—for example, a cardiac anomaly—is of course important, but the commonest question which the doctor will be asked has to do with the child's intellectual potential. Adopters of the professional classes often want to know not only that the child is free from definite mental defect but that he will not be dull or backward. Guarded as any prognosis on these matters must be, particularly where an infant is concerned, it is helpful in attempting it to take into account the following factors: (1) the prenatal and paranatal history; (2) the occupations and achievements of the child's parents and near relatives; and (3) the evidence from long-term follow-ups of adopted children.

If the health of the mother has been perfectly normal during pregnancy, and if the infant's birth, birth weight, and behaviour during the first three weeks were normal, the chances of its showing a serious mental disability are small. The elaborate studies of Knobloch and Pasamanick (1959) in the United States and of Douglas and Blomfield (1958) in this country lend powerful support to the view that children judged to be premature because of low birth weight tend to be backward in their education later on, and that any child who shows signs of cerebral damage in the first year of life has a poorer outlook for intellectual development. In these two groups of children, therefore, an expert opinion may be helpful to the practitioner who has to advise the would-be adopter.

The occupational status and achievements of the child's parents and their relatives, together with an appraisal of their health, are commonly taken into consideration, in an attempt to exclude familial types of mental illness, defect, or dullness. It is tempting in view of the fairly high correlation between the intelligence of children and that of their parents to assume that a child will grow up to be roughly the equivalent of his parents in intellectual stature, and that this will provide a guide when selecting a child for would-be adopters who would prefer him to be of their own sort. There are, however, many pitfalls in this reasoning, especially if, as is commonly the case, the parents' intelligence is inferred from their occupation. Moreover, the children available for adoption—practically all of them illegitimate—come from families covering a much wider occupational and social spectrum than do the adopters. In an analysis I recently made of 100 consecutive children offered for adoption to a large adoption society and of 100 consecutive applicants wishing to adopt a child, the distribution of social class in the family of the child's mother (recorded from her father's occupation and in 10 cases from her own occupation) was the same as that in the general population in the 1951 census, whereas the adopters showed a predominance of persons in social classes 1 and 2 (see Table).

There is a good deal of evidence that children of inferior social backgrounds placed early with good adoptive parents of superior socio-economic status show a significantly better achievement than would be expected from their natural parents' performance, and a substantial number are found by adolescence to have developed average or above-average intelligence. In one

Social Class of Adopted Child's Parents; and of Male Adopters in 100 Consecutive Cases of Each Reaching an Adoption Society in 1958

Social Class (Registrar-General)	Child's Mother Assessed from Her Father's Occupation	Child's Putative Father Assessed from His Occupation	Male Adopter Assessed from His Occupation	Population of England and Wales. Census 1951
1	3	7	15	3
2	19	5	38	15
3	53	57	36	53
4	13	13	11	16
5	12	12	0	13
Unknown	—	6	—	

of the well-known Iowa studies by Skodak and Skeels (1949), based on 63 natural mothers and their children placed early in superior adoptive homes, the average I.Q. of the children at adolescence was 20 points higher than that of their true mothers. In another study from the same research centre (Skeels and Harms, 1948) the illegitimate children of mentally deficient women placed in infancy with socially above-average foster-parents were found when tested at about 5½ years to have a normal range of intelligence, some with subnormal and some with very high I.Q.s, but most of them developing normally and not according to prediction.

It is clear that the character of the home in which the child develops strongly influences his final intellectual functioning whatever advantages he may bring from his genetic endowment (evidence about which is usually scant) and that the emphasis should be placed on the character of the adopters and their capacity for parenthood in the fullest sense.

The Adopters

Medical examination of the adopters will normally be straightforward or difficult according to the degree of the doctor's acquaintance with their medical history in all its aspects. But two problems confront him in every case: What medical criteria are suitable for judging whether people can be entrusted with an adopted child? and What right has he to disclose to an adoption society or other body confidential information about the "physical, mental or emotional" condition of his patients? Since in almost all cases the adopters give the doctor permission to supply to an adoption society all relevant information, the latter problem seldom perplexes the practitioner; but in judging whether persons with such-and-such psychological troubles or chronic physical defect can be considered suitable as adopters, he must rely on his common sense and insight, for there are few assured principles based on systematic follow-up inquiries and research. His dilemma in most such cases is less awkward if the doctor is dealing with an adoption agency rather than himself acting as the "third party" arranging the adoption.

The larger adoption societies have much accumulated experience, and have medical advisers specially acquainted with these issues: so long as the practitioner provides details of his examination findings and, wherever possible, data bearing on the applicant's past medical history, both physical and psychological, the adoption society takes the actual decision to accept or to refuse the application without disclosing its reasons. In thirteen years as a member of an adoption committee now dealing with more than 500 adoptions a year, I have been impressed by the fullness and value of the reports, often embodying consultants' opinions, supplied by doctors, which make fairer decisions possible. This has been helped by the society's use of detailed medical forms. It is, of course, not only the medical findings that have to be taken into account and carefully weighed, but also social data ascertained by the adoption society's social staff. Sometimes utterly unexpected and disconcerting information turns up on what seems a medically impeccable applicant, to the effect that he has a criminal record or has even been found guilty of cruelty or sexual offences against children.

Third-party Adoptions

Doctors sometimes act as intermediaries in an adoption, without a registered adoption society or local authority being involved in the placement. The Adoption Act recognizes such activity, whether by doctors or any other person, and stipulates the procedure then appropriate. A doctor is so clearly in a strategic position to know about both a newly born child whose mother wants it adopted and about a couple who would like to adopt a child that he is under strong temptation to act as "third party." Even though he must in any case give notice to the local authority of his intention to place the child and, under the new Act, could be called on to appear before the court when the adoption is to be ratified, the long-established role of the doctor in these matters will probably not be given up wholesale. It must, however, be admitted that the system has not worked very well in certain areas, and that it has intrinsic weaknesses. The B.M.A. drew attention to some of them when it offered evidence to the Hurst Committee.

Light was thrown on this matter by the replies to a questionary distributed by the Standing Conference of Societies Registered for Adoption last year. Nineteen societies replied. They had been asked to indicate how third-party adoptions through doctors and nursing homes had worked within their knowledge. Their replies described three categories: (*a*) intervention to effect an adoption which had been refused by an adoption society; (*b*) "two-way traffic," especially by obstetricians and gynaecologists who knew both of a child to be adopted, and of a couple who wished to adopt; and (*c*) hasty placements direct from hospital or nursing-home, in which the doctor acted without making adequate inquiries into the fitness of the adopters or full inquiries into the circumstances of the infant's mother.

There is clearly room for difference of opinion between a doctor and an adoption society about the suitability of applicants, and no one is entitled to question the conduct of a doctor who acts on his convictions, provided that he takes due care to satisfy himself that the future welfare of the child is safeguarded.

There are other considerations, too. Moral welfare workers associated with adoption societies often undertake social work with the unmarried mothers of adoptive children to assist them to meet the material and emotional stresses of their situation, and are thereby often able to lessen the chance that they will fall again into the same predicament. Doctors acting quite independently as third parties—especially when they are not the regular medical advisers of the would-be adopters or of the unmarried mother—have not the resources needed for such work, and are, in many

instances, meeting only the immediate demands of the mother or of the adopters.

Doctors acting as third party and placing a child within its first six weeks are likely to be influenced by the widespread belief that psychiatrists have demonstrated serious consequences to ensue whenever a baby is not steadily in the care of the same mother or "mother substitute" from birth: deprivation of love from a mother figure in the first year of a child's life is supposed to be fraught with danger of a warped affectionless personality, delinquency, or mental disorder in later life. These fears are exaggerated and still without solid foundation. Though there are some advantages to both the adopters and the child to be derived from early placement, the risks of entrusting a possibly handicapped child to unsuitable adopters are at least as great as letting a child be with its natural mother for a few weeks or months after birth, while the adoption arrangements are being proceeded with.

Kindness of heart plays a large part in prompt third-party placings. The doctor, or it may be the nurse, wishes to relieve the unmarried mother's distress, and promises during the pregnancy to get the child adopted as speedily as possible, perhaps undertaking that the mother will never see the unwanted and unwelcome child. The baby placed with adopters hastily a day or so after birth is often insecure. The adopters may be overanxious when they get a newborn child, and, at the first sign of its being sickly, wish to reconsider its suitability: conversely, the child's mother may have taken the decision without reflection or guidance, immediately after the baby's birth or in the late stages of pregnancy, during which she was anxious and ashamed. She was perhaps mistaken in her gloomy estimate of how her family would react to her situation; she may now wish to keep her child. If the adopters, on the other hand, return the child she is confronted unprepared with the problem of finding accommodation for herself and the child; she may be driven to hand the child over to some casual foster-parents. It is a predicament less likely to occur when the adoption has been effected more deliberately and with fuller preliminary inquiries. The child hurriedly dealt with is in a worse position than if, before the adoption had been put in train, there had been a few weeks of supervision of the child's condition and behaviour, with its mother or in a foster-home or nursery developed for the purpose, as would commonly be the case if an adoption society were responsible.

It is, of course, true that third-party adoptions effected by doctors immediately after the baby's birth sometimes turn out well, and that adoption societies' adoptions sometimes turn out badly. There are, however, grounds for believing that the risks for the child, and for the adopters, are greater when a third-party adoption is effected a few days after birth, or when the adoption is arranged without adequate inquiry into the natural mother's situation and into the social and psychological as well as medical characteristics of the adopters. The practitioner acting as a third party is therefore on much safer ground if he calls in the help of a trained social worker. Such steps are, however, superfluous if he is acting as medical examiner under the provisions of the Adoption Act, or forwarding his report to an adoption society or local authority. The closer the contact between doctor and adoption agency the better for the child, its mother, and its adoptive parents.

It is a regrettable fact that the adoption societies do not cater for the whole community. Almost without exception they are supported by religious bodies and restrict their placements to applicants who declare themselves to be practising adherents of some religion. Facilities for would-be adopters who have no religious affiliation are insufficient, no matter how well suited they may be otherwise to fulfil the obligations of an adoptive parent. The new Act encourages the children's departments of local authorities to act as adoption agencies: it may be that their activity will remedy the defect, though, of course, if the child's mother has expressed a wish for the child to be brought up in a specified religion her wish must be implemented.

The adoption societies are broadening their views in some respects in accordance with changing standards and fresh knowledge about children's development and heredity. While this advance is occurring, there is unfortunately no concurrent lessening to be discerned as yet of the activities of those third parties who place children for adoption in large numbers. They are often people in charge of private nursing-homes or organizers of "centres," who arrange for the children of unmarried mothers delivered in their homes to be adopted, and who appear to do this on such a large scale that it could almost be regarded as a business (though doubtless the provisions of the law, which forbids payment for an adoption, are observed). The administrative officer of the children's department of the Surrey County Council (Pring, 1958) has drawn attention to this trouble, which is well known to children's officers, the moral welfare associations, and to the National Council for the Unmarried Mother and her Child. Though, of course, doctors are not involved in this type of third-party activity, it is probably in their power to discourage it actively if it comes to their knowledge in the case of girls who are under their professional care during pregnancy or afterwards. The requirement in the 1958 Adoption Act that the mother of a child placed for adoption must name the person who introduced her child to the adopters—that is, as third party—will militate against wholesale adoptions of this kind or, at least, enable them to be detected by the magistrate or judge, who is entitled to call on such persons to appear at the court hearing.

Conclusion

The new Adoption Act offers opportunities for helpful collaboration between practitioners and social workers in using the ancient and humane device of adoption. In the past there has been some misunderstanding about the doctor's role in this field. This article is designed to outline some relevant features of the new Act which will affect him and to stress the advantages of collaboration between the doctors and the adoption agencies. It would be a step forward if more doctors were to serve on the case-committees which each adoption society must appoint to examine all proposed adoptions.

REFERENCES

Adoption Act, 1958. H.M.S.O., London.
Douglas, J. W. B., and Blomfield, J. M. (1958). *Children Under Five*, p. 138. Allen and Unwin, London.
Gibbs, N. K., and Woolf, L. I. (1959). *Brit. med. J.*, **2**, 532.
Knobloch, H., and Pasamanick, B. (1959). *J. Amer. med. Ass.*, **170**, 1384.
Lancet, 1959, **2**, 553.
Pring, H. W. (1958). *Child Adoption*, No. 27, p. 20.
Skeels, H. M., and Harms, I. (1948). *J. genet. Psychol.*, **72**, 283.
Skodak, M., and Skeels, H. M. (1949). *Ibid.*, **75**, 85.

ADRENERGIC MECHANISMS

[FROM A SPECIAL CORRESPONDENT]

A symposium on adrenergic mechanisms was held in London on March 28 and 29. The proceedings were opened by Sir HENRY DALE, F.R.S., who said that it was T. R. Elliott who, in 1904, started the idea that adrenaline might be one transmitter of the nervous impulse in the autonomic system. H. H. Langley, who disliked theories and was wont to say that if facts were collected the theories would make themselves, was discouraging. Later Elliott collaborated with Dale, who was then working on the adrenaline antagonist ergot. Dale himself at that time studied noradrenaline, which he regarded as a curiosity and whose properties caused him to hesitate to accept Elliott's theory. Noradrenaline, however, many years later, turned out to be more than just a curiosity when Bacq proposed it as the chemical transmitter, rather than adrenaline. It was Loewe who elegantly demonstrated, on the frog's heart, that there were two chemical transmitters and established the theory of chemical transmission firmly.

Background Physiology

Dr. H. J. SCHÜMANN (Frankfurt) described the formation of adrenergic transmitters through the chain tyrosine→dopa→dopamine→noradrenaline→adrenaline. Dr. J. AXELROD (Bethesda, U.S.A.) described the disposition in the body of adrenaline and noradrenaline. There was no convincing evidence of how noradrenaline is destroyed in the intact animal. It was likely that the enzyme catechol methyl transferase is more important than monoamine oxidase. Dr. M. SANDLER (London) said that vanillyl mandelic acid (V.M.A.) is a metabolite of adrenaline whose presence in the urine can be used as a diagnostic test for phaeochromocytoma. He thought it might be superior to the estimation of adrenaline and noradrenaline for this purpose.

Dr. H. BLASCHKO (Oxford) wanted to be told why the adrenal cortex and medulla were so closely associated anatomically. He suspected that it must be by design, but could not see why at present. Professor J. D. BOYD (Cambridge) described the origin of chromaffin tissue in the embryo from cells of the neural crest and perhaps the ventral roots. Dr. P. B. HAGEN (Winnipeg) discussed the storage of catecholamines in chromaffin granules. Dr. J. H. GADDUM, F.R.S. (Cambridge), described the peripheral sensitization to noradrenaline that occurs when adrenergic nerves are depleted of their stores of noradrenaline. It seemed similar to the sensitization that follows nerve section.

Sir LINDOR BROWN, F.R.S. (London), described the liberation of noradrenaline from nerve endings by stimulation. It was unaltered by inhibiting enzymes presumed to destroy noradrenaline in the body. He thought that combination of noradrenaline with receptors might have to precede destruction.

Bretylium and Guanethidine

Dr. W. A. BAIN (Welwyn) described the development of the first chemical which actually prevents the release of noradrenaline by the adrenergic nerves, T.M.10. Unfortunately it had many other properties and could not be used in chemical practice. He thought such substances should be called "anti-adrenergic" and distinguished from the anti-adrenaline drugs, which do not prevent release of the transmitter but antagonize it after release.

Dr. A. F. GREEN (Beckenham) described the development of bretylium ("darenthin"), which acted like T.M.10 on the adrenergic nerves, but which was free from the other undesirable effects so that it could be used to reduce sympathetic activity in man. The blocking effect of bretylium was preceded by brief stimulant effects, and there was an increased peripheral sensitivity to noradrenaline. The adrenal medullary production of adrenaline and noradrenaline was not blocked. Dr. H. J. BEIN (Basle) described guanethidine ("ismelin"), which has effects similar to those of bretylium.

Dr. JEAN GINSBURG (London) discussed the effects of adrenaline, noradrenaline, and isoprenaline on some peripheral blood vessels. Noradrenaline was predominantly vasoconstrictor, isoprenaline was a vasodilator, and adrenaline first dilated and then constricted. Dr. Z. BACQ (Liége), in reply to a questioner, briefly described some vascular responses in the common South American sloth.

Dr. D. R. LAURENCE (London) described the clinical effects of drugs which prevent the release of the adrenergic transmitters, bretylium and guanethidine. Their effects in man were similar to those in animals. Bretylium could cause a rise of blood pressure in the presence of phaeochromocytoma, and a common side-effect was pain in the parotid gland. No completely satisfactory explanation of this pain was forthcoming at the discussion. The chief difference between bretylium and guanethidine was in the duration of action of guanethidine, which was much longer. It was possible that there is less tolerance with guanethidine. Dr. C. T. DOLLERY (London) thought guanethidine was probably superior to bretylium because tolerance was less, absorption from the gut was greater, and the dose was smaller. The sheer size of the bretylium dosage was important to patients if not to pharmacologists. Dr. R. W. D. TURNER (Edinburgh) gave his experience with bretylium. He was becoming disappointed with it.

Adrenaline's Mode of Action

Dr. EDITH BÜLBRING, F.R.S. (Oxford), described elegant experiments to show how adrenaline worked. She thought it had a dual action on the cell membrane and on intracellular metabolism. It caused sodium to leave the cell, and reduced sodium uptake by the cell. It also entered the cell and increased energy production. In the case of smooth muscle most of this was taken up to stabilize the inherently unstable cell-membrane, whereas with voluntary muscle, whose membrane was inherently stable, the energy was available to assist contraction. This explained how adrenaline inhibited intestinal muscle and enhanced contraction of voluntary muscle. All this was supported by experiments of the greatest elegance, including the substitution of lithium for sodium. Lithium, it seems, can enter the cell like sodium, but cannot leave it. Therefore adrenaline would not be expected to work on the cell; it did not.

It was pointed out that Bülbring's experiments might be complicated by the reactions of nervous tissue existing in the intestinal muscle. She had thought of that, and said that her preparations contained no nerve cells.

Professor J. H. BURN, F.R.S. (Oxford), described experiments suggesting that some sympathomimetic drugs act by causing a release of noradrenaline from stores in the tissues rather than by a direct action. He instanced their failure to act after tissue stores had been depleted by reserpine administration, and recovery of action after their replenishment by noradrenaline infusion. His theory was subjected to criticism, but he remained undaunted and resourceful.

Central Effects

Dr. MARTHE VOGT, F.R.S. (Edinburgh), opened the final session on central adrenergic mechanisms by asking why intravenous adrenaline caused arousal and intracerebral adrenaline caused sedation. Was the effect of intravenous adrenaline related to blood pressure and other peripheral changes? The symposium concluded without her being much wiser on this point.

Professor W. FELDBERG, F.R.S. (Mill Hill), described his experiments injecting adrenaline into the cerebral ventricles of cats, and related them to the known sites of noradrenaline storage in the brain. Dr. P. DELL (Paris) described the effects of adrenaline on the brain stem after intravenous injection, causing arousal. Dr. H. WEIL-MALHERBE

(Wickford) said that adrenaline and noradrenaline do not penetrate the blood–brain barrier except at the hypothalamus. He had shown this, using radioactive adrenaline and noradrenaline. Dr. C. M. WILSON (Liverpool) said there was no blood–brain barrier at all in the area postrema and in the pituitary region.

Dr. A. CARLSSON (Lund) showed that inhibitors of monoamine oxidase cause an increase in catecholamines in the brain. Dr. R. T. C. PRATT (London) described the clinical effects of monoamine oxidase inhibitors ("marsilid," "nialamid") on psychiatric patients. They reduced depression and might cause excited states. Their value was as yet unproved. An important and little-recognized difficulty in psychiatry was the doubt about the homogeneity of the diagnostic groups. Endogenous depression, for example, might be due to a variety of factors, including genetic differences. He thought responses to monoamine oxidase inhibitors might be genetically determined.

The symposium was organized by the British Pharmacological Society with co-operation from the Physiological and Biochemical Societies and the Royal Society of Medicine. It was succeeded by a smaller symposium on the same subject at the Ciba Foundation. The proceedings of both will be published in one volume by Messrs. J. and A. Churchill, London.

Nova et Vetera

HARVEY—A DWELLER IN TWO WORLDS

It is important and right, and justly numbered among the acts of piety, to seek to know all we can of Harvey. Mrs. Whitteridge's edition and translation of his notebook *Of Local Movement of Animals* is beyond reproach for clarity and arrangement.* It contains a real addition to our knowledge of Harvey, though the reviewer would need even more persuasion than hers to convince him that his handwriting was good for its day or was uniform in its eccentricities. But this book is very useful in bringing out an aspect of the man that has been too little emphasized. It was well known that Harvey was by temper conservative, but the degree to which he, who advised us "to seek out the ways of nature by experiment," was ruled by his temperament has perhaps hardly been appreciated. Thus in the course of 69 small quarto pages of print here he mentions or quotes Aristotle more than 100 times, Galen about 60, and no modern writer extensively except Fabricius and Spigelius, both of Padua. He mentions Laurentius (once), Vesalius (once) and—save the mark—the Rosicrucian Robert Fludd (once). The last is important for the history of human error, but can have no place in the history of science. The atmosphere of this document of Harvey is so mediaeval that many of its pages—perhaps most of them—might have been written at Salamanca in the fourteenth or fifteenth century. If this were all we had of Harvey and if the English words and modern names had been removed, it would have been hard to believe that it was the work of a well-educated, well-travelled, and well-to-do English physician, who had studied at Padua, then in the van of scientific progress, who had produced the greatest work of experimental physiology of his century and perhaps of any century, who had mingled with some of the most intellectual society of his day, and who was contemporary with Francis Bacon, Descartes, Gassendi, Mersenne, Galileo, and Stevin.

Did this extremely conservative mentality of Harvey affect his influence? I rather think that it did. It is recognized that knowledge of the circulation hardly affected medical practice for a century and more after its publication. Repeated and extensive phlebotomy continued. Just in that century the Aristotelian physics—which had long been under critical fire—came under attack from Stevin, from Bacon, and from Descartes. It collapsed with Galileo, and finally disappeared with Newton. True the direction of the attack of these groups came from different angles, but during the century "Aristotelianism" became almost synonymous with intellectual backwardness. The clinical literature from 1628 onward should be reconsidered from this point of view. It would be interesting, in this spirit, to re-read Sydenham, Sylvius, and Boerhaave, for example. Nevertheless, this book is a fine piece of scholarship admirably set forth, and its exact translation tells, in plain English, something of Harvey which comparatively few knew before.

CHARLES SINGER.

*William Harvey's De Motu Locali Animalium, 1627. Edited, translated, and introduced by Gweneth Whitteridge, M.A., D.Phil., F.S.A. (Pp 163+x. 60s.) Cambridge: University Press for the Royal College of Physicians. 1959.

New Appliances

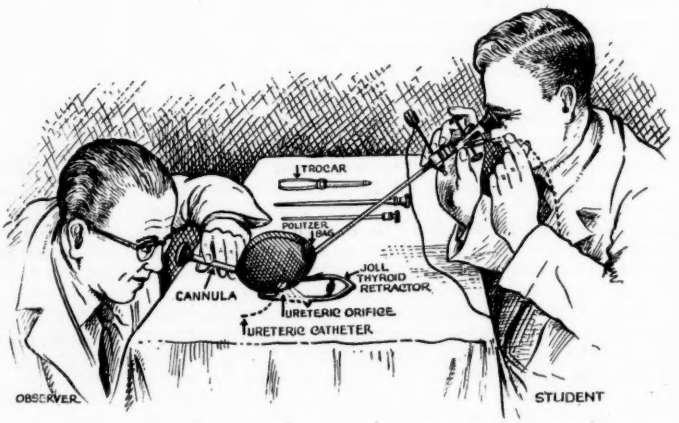
DEVICE FOR TEACHING CYSTOSCOPIC PROCEDURES

Mr. D. W. BRACEY, consultant surgeon, Memorial Hospital, Peterborough, writes: The subject of simple cystoscopic procedures is often difficult for registrars and residents to grasp. It might be of interest to your readers to describe a device I use to teach not only the function of different instruments but, equally important, the essential landmarks in the bladder and how to see and reach them. The materials required are: a Politzer bag, a large-size thyroid retractor (Joll), and a bladder trocar and cannula.

The Politzer bag has both its entry and exit tubing cut off flush with the bag, and 1¼ in. (3.8 cm.) from one end an oblique slit is cut in each of the two underseams. These slits represent the intramural portions of each ureter. Half-way along these seams the teeth of the thyroid retractor are made to engage the bag so as to steady it as it lies on the top of a cystoscope cabinet, which is covered by a green theatre towel. The cannula is made to penetrate the entrance hole into the bag furthest away from the slits already made (see Fig.).

The surgeon and student sit or stand opposite each other; an instrument is selected from the cabinet and its mechanism explained. The student then inserts the cystoscope through the hole in the end of the bag facing him, and, under the guidance of the surgeon watching through the cannula from the opposite end, manœuvres the instrument inside the

(*Continued at foot of next page*)



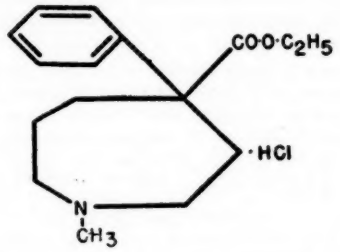
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Ethoheptazine

"Zactirin" (John Wyeth) contains ethoheptazine citrate (75 mg.), aspirin, 5 gr. (325 mg.), and calcium carbonate (97 mg.) per tablet.

Chemistry.—Ethoheptazine is 4-carbethoxy-1-methyl-4-phenylhexamethylenimine, and has the following structural formula:



Pharmacology.—Ethoheptazine is a mild analgesic chemically related to pethidine, without the constipating effect of codeine.

Therapy.—From one to eight tablets per day can be used in the treatment of a wide variety of painful states, particularly musculo-skeletal, such as arthritis; visceral, such as dysmenorrhoea; and post-traumatic, such as the pain following dental extractions.

As an analgesic ethoheptazine has been found effective in from 62% to 80% of patients with a variety of painful states. In a controlled trial[1] ethoheptazine with aspirin has been found as effective as codeine with aspirin. Ethoheptazine is said to be non-addicting, but it must be remembered that similar claims were made for pethidine when first introduced.

Toxic Effects.—None have been reported for ethoheptazine so far. The main toxic effect of therapeutic doses of aspirin is the production of dyspepsia and sometimes gastrointestinal bleeding (rarely severe). The incorporation of calcium carbonate in the tablet (and the recommendation that tablets should be taken on a full stomach) is expected to minimize these effects.

Contraindications.—Preparations containing aspirin are best avoided by patients liable to peptic ulcers or iron-deficiency anaemia.

N.H.S. Basic Price.—100 tabs. for 22s. 6d.

REFERENCE

[1] Cass, L. J., Frederik, W. S., and Bartholomay, A. F., *J. Amer. med. Ass.*, 1958, **166**, 1829.

(Continued from preceding page)

artificial "bladder." With the free hand of the surgeon to guide him in the early stages, the student soon learns his way around the "bladder" and to manipulate a ureteric catheter into each "ureteric orifice"—the slit in the underseam on each side. The normal cystoscopic lighting source is quite sufficient to light up all areas of the bag. By inserting a probe through the cannula with the tip covered with a thin pledget of wool soaked in a suitable dye, the surgeon can mark a particular spot inside the "bladder" and train the student to direct an electrode direct on to it, as though fulgurating a papilloma. Simple modifications could be made to enable the student to learn the basic principles of diathermy or punch-resection. Finally, the positions can be reversed and the student watch the surgeon manipulating any particular instrument.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Diffuse Interstitial Pulmonary Fibrosis

SIR,—Dr. J. G. Scadding (February 13, p. 443) produces reasonable arguments for rejection of chemical irritation as a cause of interstitial pulmonary fibrosis, but an experience during the war makes me uncertain whether such a cause can be absolutely excluded. In 1944–5, as consultant physician to the Australian Army, I encountered six patients with severe interstitial pulmonary fibrosis, of whom to my knowledge three died within the year. Four of these six cases had evidence of mepacrine (atebrin) excess or sensitivity. Two patients were in hospital because of a severe lichen planus type of dermatitis which was known to be associated with mepacrine sensitivity. Two others had no skin lesions, but showed intense mepacrine staining with yellow conjunctivae and black pigmentation of the mouth. The remaining two patients had no evidence of mepacrine toxicity, but their symptoms had occurred after mepacrine administration had been continued for two to six months, and one patient states he had more mepacrine than the advocated amount of 0.1 g. daily.

Progressive breathlessness was the symptom of which the patients complained. Two severe cases showed marked cyanosis. There was no evidence of heart disease, except in one patient who developed terminal right heart failure. *X*-ray films showed fibrosis, extending from the hilus to the periphery, with the upper lobes relatively spared. Post-mortem examination in two cases showed intense interstitial fibrosis of the lungs. None of the commoner causes of pulmonary fibrosis were present.

Unfortunately, it was not possible to publish these observations because the importance of mepacrine administration as an anti-malarial agent was such that military policy did not permit publicity for any of the few side-effects of mepacrine ingestion. Post-mortem specimens were lodged with one pathology department for investigation after the war ended, but regrettably were lost during reorganization of the department.

These findings, together with the recognition of pulmonary change due to hexamethonium, suggest that a chemical aetiology for the type of pulmonary fibrosis described by Dr. Scadding cannot be excluded. The relatively high incidence described in rheumatoid arthritis—a disease in which varying drugs are used over a long period—would be compatible with the possibility that such changes may be due to ingested, and not inhaled, chemical irritants.—I am, etc.,

Department of Medicine,
University of Melbourne.

J. G. HAYDEN.

Hospital Infection and Visitors

SIR,—When the patients to be visited are young children, the risks of infection introduced or spread by visitors (February 20, p. 563; March 19, p. 878) must be carefully weighed against the risks of emotional disturbance caused by the mother's absence. The need for daily visits by mothers of severely burned children has been emphasized in a recent report by Mrs. J.

Woodward[1] on patients who were treated in this hospital. Pickerill and Pickerill[2] have described a special hospital where mothers were admitted to help in the nursing care of their children, and reported an absence of cross-infection, which they attributed to this method. Provided the mother stays with her own child, her visits should at least present no extra hazard of cross-infection, though she may bring in streptococci and certain viruses which are likely to cause infection.

With these considerations in mind we have, since the later months of 1957, encouraged parents to visit their children daily for half to one hour in the burns unit of this hospital—a reversal of our former policy of restricting visits to a minimum. The parents are asked to stay away if they have colds, boils, or other infection, and are requested not to visit any children except their own. If their child is extensively burned or infected with *Streptococcus pyogenes* or *Pseudomonas pyocyanea*, the parent is issued with a cotton gown to wear while attending the child, a rule extended now to all visitors.

Infection of Burns in a Ward Before and After the Introduction of Parents' Daily Visits to Small Children

Year	Daily Visits by Parent	Mean Monthly % of Patients whose Burns Acquired		No. of Patients in Ward
		Str. pyogenes	*Ps. pyocyanea*	
1955–6	No	13·9	25·8	499
1956–7	,,	23·3	24·4	465
1957–8	Yes	14·3	24·1	447
1958–9	,,	13·4	22·8	458

We have recorded the monthly incidence of added infection with *Str. pyogenes* and *Ps. pyocyanea* obtained from routine bacteriological sampling of all burns in the ward. The data for a period of two years before and two years after the introduction of daily visits by parents is summarized in the Table; this shows no increase in infection with either organism, and the lowest incidence was actually recorded in the year 1958–9, when the children were receiving daily visits.

The comparison of data from different periods of time is, of course, imperfect by the standards of controlled trial. For example, the burns of some patients in the ward during the period 1956–7 were dressed with tulle gras, which has been shown to allow more frequent colonization of the burns with *Str. pyogenes*[3]: this is reflected in the higher incidence of streptococci during that period. But no changes likely to affect the incidence of *Ps. pyocyanea* were introduced, and added infections with that organism were remarkably constant during the four years of the study.

It is, perhaps, improper to generalize from this experience in the burns unit of an elderly hospital; in wards where cross-infection is a rarity the results might possibly have been different. But our findings suggest that visitors whose movements are supervised do not appreciably increase an already substantial hazard of cross-infection.—We are, etc.,

E. J. L. LOWBURY.
D. MACG. JACKSON.

Medical Research Council Industrial Injuries and Burns Research Unit, Birmingham Accident Hospital, Birmingham, 15.

REFERENCES

[1] Woodward, J., *Brit. med. J.*, 1959, **1**, 1009.
[2] Pickerill, C. M., and Pickerill, H. P., *Lancet*, 1954, **1**, 425.
[3] Cason, J. S., and Lowbury, E. J. L., ibid., 1960. In press.

Side-effects of Phenelzine

SIR,—In the past five months I have administered "nardil" (phenelzine dihydrogen sulphate) to 34 in-patients and 12 out-patients, usually for pure depressive states of moderate to severe degree. I have been most impressed on the whole with the results, and many patients have been remarkably improved. However, I have experienced certain side-effects which I would like to bring to attention.

All the following complications developed during the first week or ten days of treatment, and all cases received the manufacturer's indicated dose—that is, 75 mg. a day in divided doses. I have found oedema to be rather common, but in one case severe oedema of the glottis developed with dyspnoea.

In one case a middle-aged woman developed palilalia, and three other cases developed ataxia of severe degree and went completely off their legs. In the latter three the clinical signs were those of marked clonus and spasticity of the lower limbs with up-going toes. A further case developed "wobbly legs" without physical signs, but complained bitterly of "woolly thinking" and forgetfulness.

A further two cases developed a toxic delirium. One of these was a nocturnal type of delirium and was associated with choreiform movements and a coarse extrapyramidal tremor. The remaining case was remarkable in that she developed a mescaline-like psychosis with vivid hallucinatory experiences and distortion of perception, depersonalization, and desomatization. The associated physical signs were those of nystagmus, ataxia, and altered pain appreciation of the thalamic type.

The initial conclusions from my first short trial are that phenelzine is an extremely effective drug in the treatment of pure depressive illnesses, but that the original dose of 75 mg. a day recommended by the manufacturers is probably far too high, at least for some patients. In none of my cases was there any question of any permanent disability, and all the side-effects noted disappeared when the drug was discontinued.—I am, etc.,

J. CLARKE.

Saxondale, Hospital, Nottingham.

Lenticular Implants

SIR,—Your annotation (April 2, p. 1037) was interesting but misleading in some respects. Firstly, it is wrongly titled—the posterior chamber lens of Ridley was designed specifically to correct the optical defect occurring in aphakia. The anterior chamber implant is not lenticular in shape and can correct this condition and many other conditions besides, such as the provision of an artificial pupil, to assist in penetrating keratoplasty, and so on, as I have recently demonstrated.[1 2] A better title would have been "The Effects on the Eye of Intraocular Acrylic Implants."

Your annotation goes on to say that "the final answer must wait many years, but the first pathological study of such an eye has recently been published[3]; and it should curb the exuberance of some of the more determined lenticulus-implanters." As one of the most enthusiastic "anterior chamber implanters" in the country, I hasten to say that our findings have certainly not curbed my enthusiasm. During the 18 months which have elapsed since I knew of Ashton's findings I have been responsible for the insertion of a further 150 implants on patients under my care. Indeed, the findings provided me with the priceless reassurance that sympathetic ophthalmia was a most unlikely probability,

which was, until then, one of my basic worries. The eye in question was the sixth in my series, which now exceeds 250. In those days, over three years ago, I still had much to learn about the design of the implant, its sterilization, and the technique of its insertion into the eye. I very much doubt if a similar specimen to-day would show quite the same amount of pathology.

Your annotation singles out aphakic eyes in this context; this is an interesting point. For various reasons I have inserted implants into about 30 phakic eyes. There have been no complications in these, whereas there have been certain complications, some explicable, some not, in my aphakic cases, which leads me to feel that we do not know as much as we should about the natural history of the aphakic eye. I think there is scope for a large-scale clinicopathological survey of aphakic eyes which have not been subjected to implant surgery.

I have observed that when many years have elapsed between cataract surgery and insertion of the implant the results are always excellent. I cannot recall a single disappointment in this category. I am therefore inclined to agree with you that results might be better if there was a longer interval between cataract extraction and implant surgery than the 6 to 8 weeks which I have recommended until now. I also agree that we should "avoid subjecting too many healthy aphakic eyes to dangers which we cannot truly apprehend until several more years have passed," but mainly because I disapprove of surgeons doing this sort of work in a casual, once-or-twice-a-year sort of spirit. One cannot hope to succeed with difficult operations on this sort of basis, and yet that is what does tend to happen with a new technique. I am in favour of surgeons who are interested dedicating themselves to investigating personally this method, which, when used correctly on correctly chosen cases, brings such benefit to the patient. Finally, I too have heard that "life is short . . . experience fallacious, and judgment difficult," but two can play at this game. I quote our illustrious President, H.R.H. the Duke of Edinburgh, who recently declared, in his own forthright fashion, that "if anybody has a new idea in this country, there are still too many people who advocate putting a man with a red flag in front of it."—I am, etc.,

London, W.1. D. P. CHOYCE.

REFERENCES

[1] Choyce, D. P., *Lancet*, 1960, **1**, 90.
[2] —— *Trans. ophthal. Soc. U.K.*, 1960. In press.
[3] Ashton, N., and Choyce, D. P., *Brit. J. Ophthal.*, 1959, **43**, 577.

Dihydrostreptomycin Deafness

SIR,—I was, perhaps somewhat naively, surprised to learn from your annotation (April 2, p. 1036) that dihydrostreptomycin, at any rate in this country, still has a place in the workaday pharmacopoeia. I fondly believed that its capacity to cause irrevocable deafness was well enough known, and that it was never used either alone or in combination with other drugs. Over eight years ago an annotation appeared in the *Lancet*,[1] under the title "Deafness from Dihydrostreptomycin," reviewing the then already formidable list of adverse case reports, and concluding that dihydrostreptomycin should be discarded, since in any event it was not more potent than streptomycin in the treatment of tuberculosis.

I was further surprised to learn that the drug is still in use in the United States, as the weightiest indictment of its use came from that country, and much of it was supplied by the results of clinical trials carried out by the Veterans Administration. The most tragic feature of dihydrostreptomycin deafness is the lack of any warning that a toxic effect is occurring or likely to occur. The deafness may not appear until days or weeks after the administration of the drug has been stopped. That the drug should be combined with other antibiotics and given for the trivial conditions mentioned in your annotation is proof enough of the distance we have travelled along the road of abuse of antibiotics.

By some curious quirk of organic chemistry, whilst dihydrostreptomycin acts by destroying hearing, and rarely affects balance, streptomycin acts in exactly the reverse manner. Labyrinthine disturbances are a fairly common toxic effect of streptomycin, although fortunately they are usually only temporary. However, they can be permanent, and the labyrinth can be totally destroyed. This knowledge has been used to treat cases of Ménière's disease in which the lesion is situated in both ears, and many cases of both calculated and inadvertent destruction of the labyrinth by means of streptomycin have been reported in the past ten years. What is perhaps not so commonly realized is the occasional lack of compensation which may follow this labyrinthine damage. Usually, after a period of ataxy, the other factors subserving balance and posture gradually assume the whole function, and no permanent disability remains. Sometimes, however, this ataxy lasts much longer, and very occasionally it may be permanent. Several cases of this kind have gone to the Law Courts, and fairly recently in one such case substantial damages were awarded. Streptomycin fortunately usually gives some warning of the damage it is about to cause, and if the premonitory symptoms of slight vertigo and nausea are noticed, and the administration of the drug stopped, the damage may be avoided. Streptomycin is far too useful a drug to be abandoned without a struggle, and the combination of penicillin and streptomycin is often extremely valuable. As streptomycin damage can be avoided by careful observation of the patient's symptoms, a legal ban on its use either alone or in combination would be unfortunate. However, no such reservation need be made in dealing with dihydrostreptomycin, which should most certainly be banned by law.—I am, etc.,

London, W.1. MAXWELL ELLIS.

REFERENCE

[1] *Lancet*, 1952, **1**, 91.

Students' Acceptance of Psychiatry

SIR,—Dr. Denis Hill in his article on "Acceptance of Psychiatry by the Medical Student" (March 26, p. 917) feels that physical determinism is not an entirely satisfactory hypothesis for explaining human behaviour, normal or abnormal. This surely is not completely true. The theories of psychological determinism and cultural determinism are not incompatible with physical determinism. Our greatly increased knowledge about the way in which our behaviour is dependent upon the electrical and chemical processes going on in our brains is surely proof enough that human behaviour is in the last analysis as much physically determined as is the action of the heart. The work of the sociologist, psychoanalysts, and psychologists do not in any way contradict this, for the emotional interchanges between individuals and groups which is the raw material of their researches must have their physiological effects on the brain, for without brain chemistry we cannot have

emotions. "Emotional" causes and organic causes of behaviour are different aspects of the same process.

Our problem is that in the present state of our knowledge we are unable to provide a simple theory of human behaviour couched in the language of only one discipline. The cardiologist can explain his work in the one language of physiology, whereas in our field, because as yet we know so little, we have to explain human behaviour sometimes in the language of the physiologist, sometimes in that of the psychologist or even in the almost mystical language of the psychoanalyst, or, again, in terms of sociology and theology. It is this which makes the teaching of psychiatry to students so difficult, together with the fact that knowing about ourselves is in itself disturbing and likely to produce emotional resistance—something which does not occur when we have to face the facts of kidney function.

I submit that, given complete knowledge of all the facts, we should know precisely how a person will or, indeed, must behave. The doctrine of free will is a snare and a delusion. It has in fact been the cause of considerable suffering, for it is this doctrine that underlies the senseless punitive system of many penal codes. The more humane treatment of criminals has only come about since this strongly entrenched and irrational doctrine has begun to be eroded by our newer knowledge of human behaviour. Although Christian theology has exalted this doctrine of free will, scripture supports the doctrine of determinism, especially in the Pauline Epistles. Augustine, and even more so Luther, had little use for it. In fact Luther has been called the forerunner of scientific determinism. In spite of the problems, we shall only make progress in the understanding of human behaviour and the relief of suffering caused by its disorder if we can accept that the theory of determinism is as valid in this field of scientific study as in every other. I repeat there is no conflict between science and religion properly understood.—I am, etc.,

The Towers Hospital, Leicester. H. B. KIDD.

Truth about Psycho-analysis

SIR,—I greatly sympathize with the comments by Dr. W. H. Shepley (April 2, p. 1051), and the more so because I am not impressed by the contemporary tendency to popularize, and "describe in a nutshell," complex scientific and technical data that cannot adequately be digested by readers who possess little if any knowledge of the basic sciences, and none concerning the highly specialized subjects treated.

Professor H. J. Eysenck is a most eminent psychologist whose contributions are of considerable interest and value. There are, however, many in his own as in other fields who suffer from the "scientific narcissism" which prompted a German psychiatrist to identify the cerebrum (*Grosshirn*) with the "God-brain" (*Gotthirn*), and one of our foremost mathematician-astronomers to describe God as "the Great Mathematician." Psychologists, while assessing, to the best of their present knowledge, the intellectual capacity, ability, and aptitudes of the human mind, are perhaps more particularly in danger of entertaining the delusion that they hold in their hand the measuring rod of the universe, and consequently that those factors which cannot (at least at the present time) be subjected to measurement and statistical analysis, not only do not exist, but will never be proved to do so. Psychiatrists, too, have shown similar trends: that which (at least, by present methods) is incapable of neurohistological or micro-biochemical detection in the central nervous system, *ipso facto* does not (or, it may be, *should* not) exist in the mind. It was in this connexion that the distinguished psychiatrist H. W. Gruhle referred to the "school of brain mythology," according to which all psychiatric and sociological disorders could (as in Lombroso's conception) be detected physically, or in the structure of the cerebral cortex and the degree of supragranular development. In the light of the history of science, and the shadow of our ignorance, we would be well advised to cultivate humility, objectivity, and an eclectic approach combining all known methods of studying the function and dysfunction of the human mind, and of treating the latter.

As a corrective for undue narcissism on our part, whatever our subject or specialty, I would suggest the prescription of that great physician, the late Sir Robert Hutchison, for a new petition in the litany, to read (in part) as follows: "From too much zeal for the new, and contempt for what is old; from putting knowledge before wisdom, science before art, and cleverness before common sense . . . Good Lord, deliver us."—I am, etc.,

Bransgore, Hampshire. R. H. AHRENFELDT.

Quiescent Malarial Parasites

SIR,—Mr. P. G. Shute (March 5, p. 730) reported the occurrence of *P. falciparum* malaria in a patient in London who had received a transfusion of blood from a Nigerian donor who had been less than six months in this country. Speculating on the length of survival of malarial infections in untreated immigrants to the United Kingdom from holo-endemic malarious areas, he observed that knowledge on this subject is very deficient, but that existing data suggest that *P. falciparum* infections die out in six months to one year. It would seem relevant, therefore, to report the discovery of *P. falciparum* parasites in the blood of a Nigerian woman 19 months after her arrival in this country.

A 21-year-old Nigerian student nurse arrived in England from Lagos in December, 1956, married, and remained here. On June 24, 1958, when she was five months' pregnant, a routine blood count was carried out at the Royal Free Hospital. This showed her to be anaemic—R.B.C. 3,020,000 per c.mm., haemoglobin 8.6 g. per 100 ml.—and malarial parasites were observed in the Leishman-stained thin blood film. She was referred to the Hospital for Tropical Diseases for identification of the species of *Plasmodium* and for treatment. The only additional findings were splenomegaly (the tip of the spleen could just be palpated) and a reticulocytosis of 8%. Her malarial parasitaemia was not accompanied by fever, and it was evident that pregnancy and lack of challenge had caused a lowering but not a complete loss of acquired resistance (premunity) to the parasite.

Mr. Shute carried out an exhaustive examination of the original blood film in which he observed about 100 parasites. He was satisfied that the species was *P. falciparum*, of which early trophozoite stages alone were present. Professor P. C. C. Garnham, of the London School of Hygiene and Tropical Medicine, concurred with this opinion. Treatment rapidly abolished the malarial parasitaemia, the spleen became impalpable, and the blood picture improved. The pregnancy continued to term, a healthy child was delivered, and examination of smears of the placenta showed no malarial parasites.

The latest date on which this woman could have been re-infected was in Lagos prior to embarkation at the end of November, 1956. Nineteen months later, when pregnant, *P. falciparum* parasites were present in considerable numbers in the peripheral blood.

I am grateful to Dr. Helen Ferguson, who referred the patient to Dr. P. J. Fleming, of the Royal Free Hospital,

who sent the original blood films and report; and to Mr. P. G. Shute and Professor P. C. C. Garnham, who confirmed the identity of the parasite.

—I am, etc.,

Hospital for Tropical Diseases, London, N.W.1. JOHN WALTERS.

Surgery of the Hip-joint

SIR,—In his excellent article on the surgery of the hip-joint (March 19, p. 821) Mr. John Charnley, while advocating the merits of arthrodesis, stresses the alleged disadvantages of the "standard" method—that is to say, prolonged convalescence with immobilization in plaster with resulting stiffness and circulatory complications. These oft-repeated fallacies have done much to bring into disrepute one of the most satisfactory procedures in orthopaedic surgery, and they deserve comment.

In the first place it is impossible to immobilize a hip by any form of external fixation tolerable to the patient. A plaster hip-spica does not immobilize, because it does not fix the pelvis. In fact, by fixing the leg in a vice and leaving the pelvis comparatively free it ensures stress and movement at the hip. All it can do is to limit the *range* of movement at the hip. Hence the necessity of ensuring internal fixation of the hip when using the "standard" method. One can then dispense with all self-deceiving attempts at external fixation and the complications to which they give rise. This cannot be done if the fixation device is placed as shown in Mr. Charnley's article (Fig. 6a), as he rightly points out, but who would ever think of doing so? It must of course be inserted in the same line as shown in his own method (Fig. 6b). If this is done sound fixation is secured, external splinting is unnecessary, and convalescence is no longer and no more complicated, in all senses of the word, than with any other operation on the hip.—I am, etc.,

Guy's Hospital, London, S.E.1. T. T. STAMM.

SIR,—I have read the article by Mr. John Charnley on the surgery of the hip-joint (March 19, p. 821) with great interest and consider it might be of interest to report a simple method of arthrodesing hips.

The patient is placed on the orthopaedic table with the affected hip slightly adducted. Using a short Smith-Petersen incision, the anterior and superior aspects of the hip are exposed. After removal of the articular cartilage from the weight-bearing portions of the acetabulum and femoral head a hole is drilled in the femoral head parallel to the femoral shaft. Next a bed for an iliac graft is prepared above the hip. A substantial portion of the iliac crest 3 to 4 in. (7.6–10 cm.) long and three-quarters of an inch (2 cm.) deep is then resected and tapped into the femoral head (Fig. 1). By abducting the hip to the neutral position the graft is firmly forced into its prepared bed, but if necessary it may be secured to the pelvic wall by a single screw. The gap between acetabulum and femoral head is firmly packed with iliac chips. Finally, any fixed deformity may be corrected by a subtrochanteric osteotomy through a separate lateral incision. Post-operatively the hip is immobilized in a spica for 3–4 months.

So far six patients have been treated by this method (one case of quiescent tuberculosis, two cases of septic arthritis, two cases of osteoarthritis, one case of a failed arthrodesis using a trifin nail). Fusion was achieved in each case (Fig. 2). The advantages of this procedure are that it can be done quickly, that no massive metallic implants are used, and that only one operation is necessary—important considerations in these days of sepsis.—I am, etc.,

Lewisham Hospital, London, S.E.13. A. C. BINGOLD.

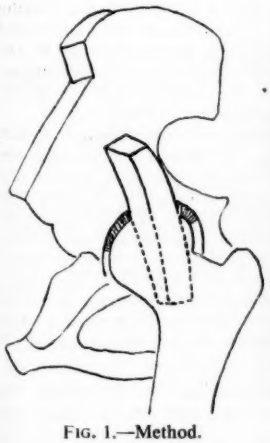


FIG. 1.—Method.

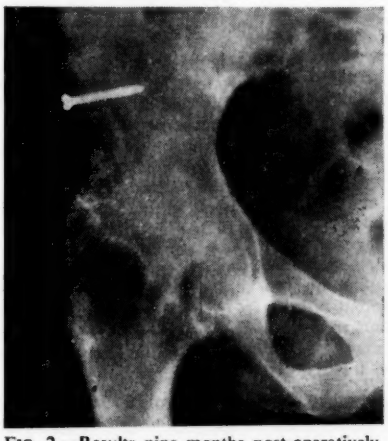


FIG. 2.—Results nine months post-operatively in a 53-year-old woman.

Diabetes in the Bantu

SIR,—Drs. W. M. Politzer, B. Hardegger, and T. Schneider (February 27, p. 615) report on the incidence of diabetes mellitus in a rural Basuto population based on a survey of out-patients attending a mission hospital. We have undertaken a similar survey of urbanized Bantu, of varying tribal origin, attending the casualty department of Baragwanath Hospital, Johannesburg, and a comparison of the results is of interest.

Our survey was confined to subjects aged 30 and over:

Age	30–39	40–49	50–59	60+	Total
Males	322	367	246	143	1,078
Females ..	458	306	157	123	1,044

Politzer *et al.* studied 3,000 Basuto varying in age from 20 to 85, but, for purposes of comparison, only their subjects over the age of 30 are considered. Among 1,742 such subjects (1,236 females and 506 males), 6 cases (4 females and 2 males) of diabetes mellitus, all previously undiagnosed, were found—an incidence of 0.34%. In our survey of 2,122 subjects, 18 new diabetics (14 females and 4 males) were discovered—an incidence of 0.85%. In addition 9 known cases (7 females and 2 males) of diabetes were detected, bringing the total to 27 or 1.27% of the series. The incidence for male and female Basuto was 0.39% and 0.32% respectively, although the validity of the male incidence is questionable in view of the relatively small number of males surveyed. Among the urbanized Bantu (considering new cases only) the male incidence was 0.37% and the female

1.34%. The rural and urbanized female populations surveyed are comparable in number and age distribution, and the explanation for the striking difference in incidence is as yet obscure. It is tempting to ascribe it to urbanization, but to do so it would be desirable to demonstrate a similar difference between rural and urbanized African males, and this must await more extensive survey studies.—We are, etc.,

H. C. SEFTEL.
G. J. ABRAMS.

Baragwanath Hospital,
Johannesburg.

Estimation of Blood Glucose

SIR,—In the method for estimating blood-glucose oxidase described by us[1] there is a tendency for the buffered enzyme-dye solution to form a fine precipitate shortly after preparation. This may be avoided, at least for several hours, by reducing the strength of the ethanolic *o*-tolidine reagent from 1% to 0.4%; colour production is substantially unaffected.—We are, etc.,

W. J. GRIFFITHS.
J. E. MIDDLETON.

Department of Chemical Pathology,
St. Thomas's Hospital,
London. S.E.1.

REFERENCE

[1] Middleton, J. E., and Griffiths, W. J., *Brit. med. J.*, 1957, **2**, 1525.

Dangers of Halothane

SIR,—May I reply to the letter of Drs. C. Langton Hewer and R. I. Ballantine (March 19, p. 876)? To incriminate the halothane as the sole reason for collapse is questionable. There appear to be other possible causes for this trouble, such as a dose of 500 mg. thiopentone with 4 ml. lignocaine hydrochloride 4% included in the induction of a patient with such a known precarious cardiac condition, possibly an unreplaced loss of blood in another, or more likely perhaps the patients were becoming deeper and deeper unknown to the anaesthetist owing to the semi-closed method of administration.

I feel that there must be some clarification of the general statements used in their first paragraph. There are two distinctly different methods of vaporizing halothane. Either by passing the patient's breath only over the drug in the closed circuit or by passing the flow-meter gases over it and using the semi-closed circuit, like Drs. Hewer and Ballantine, or the closed circuit. The safety of the former method of vaporization lies in the fact that, should the patient be given too much halothane, respiratory depression will result and therefore less and less of the drug will be vaporized. Pure oxygen will still be feeding into the circuit diluting the concentration, and a rapid fall in the blood halothane level will result together with a consequent lightening of the depth of anaesthesia.[1] Thus the patient in some measure protects himself from being given an overdose, leaving the anaesthetist ample time to retard the vaporizer control. On the other hand, the danger of the forced vaporization method with a calibrated apparatus lies in the fact that, should there be any respiratory depression, the blood concentration will continue to rise, as the inspired concentration of halothane is not reduced automatically as with the former method, thus producing a marked fall in blood pressure and serious cardiac embarrassment. I feel that Drs. Hewer and Ballantine have confirmed this danger.

It is true that a marked fall in blood pressure can occur immediately after induction with halothane, usually with ill cases, and for that matter with thiopentone, but with halothane the blood pressure will always return to its pre-anaesthetic level with 10 mg. of methoxamine and remain constant subject to blood loss or halothane overdosage. It is unfortunate that before and after induction blood-pressure figures are not given in the first case, as 10 mg. methoxamine would have quickly relieved the anxiety.—I am, etc.,

H. REX MARRETT.

Coventry.

REFERENCE

[1] Marrett, H. R., *Anaesthesia*, 1959, **14**, 30.

Suxamethonium Apnoea in Infancy

SIR,—We found the article "Suxamethonium Apnoea in an infant" by Drs. L. Kaufman and H. Lehmann and Mr. E. Silk (*Journal*, January 16, p. 166) most interesting to read. In the summary the authors state "this is believed to be the first such recorded observation in an infant." For this reason we should like to describe a case of prolonged apnoea following succinylcholine that we encountered in an infant aged 3 months.

A boy aged 3 months was admitted to hospital on December 7 with a diagnosis of intussusception. The history was that of pain beginning at 5 a.m. of the same day. This pain would last for a few seconds and then disappear. The child had vomited 14 times since 7 a.m. Bowels moved two times and had some blood in the last bowel movement. The past history and family history were completely negative for any chronic illnesses.

Weight was 15 lb. (6.8 kg.). Pulse, temperature, and respirations were all normal on admission. Physical examination revealed some rales on the left base and a hard, firm mass in the abdomen just to the left of the umbilicus. On rectal examination fresh blood appeared on the examining finger. K, 4.3 mEq/litre; Na, 141 mEq/litre; Cl, 101 mEq/litre; carbon-dioxide content, 26 mEq/litre; Hb, 13.3 g.; haematocrit, 39%; W.B.C., 8,800. Radiograph of the chest, negative. Supine and upright views of the abdomen "no gas beyond the proximal descending colon. These findings are consistent with an obstructing lesion in the descending colon, possibly an intussusception." The diagnosis of acute upper respiratory infection and an ileo-colic intussusception was made and the child brought to the operating room four hours after admission.

Atropine 1/200 gr. (0.32 mg.) was given subcutaneously at 7.30 p.m. and an infusion of 250 ml. of 5% glucose in water was started. At 9.30 p.m. anaesthesia was induced with 6 litres of nitrous oxide and 2 litres of oxygen and halothane 0.2%. 10 mg. of succinylcholine was injected intravenously and oral intubation was carried out using a French 14 non-cuffed tube. Anaesthesia was maintained with the same mixture of nitrous oxide and oxygen. Respirations were controlled via an Ayre's T-piece. At operation, an intussusception was found. This was reduced and an appendicectomy performed. The operative procedure took 90 minutes. 500 ml. of 5% glucose in water was given during the operation.

The infant was still completely apnoeic, although awake, at the end of the operation. Suctioning and moving the tube had no effect. 5 mg. of edrophonium was injected and good spontaneous breathing commenced, only to stop after 10 to 15 minutes. Thirty minutes later the edrophonium was repeated with similar results. Thereafter the patient was ventilated manually. A large amount of clear secretions requiring frequent suctioning occurred. At 12.30, four hours after the succinylcholine had been administered, the child began to breathe spontaneously. No ill-effects resulted from this complication and the child was discharged on January 3, 1960.

It would have been interesting to determine the pseudocholinesterase levels in this child, but our laboratory is not equipped to test for this readily.

Although the serum levels of potassium were normal immediately pre-operatively, the possibility of a low tissue level was present and a small amount of potassium was administered intravenously shortly before spontaneous respirations occurred.—We are, etc.,

M. MINUCK.
R. LAMBIE.

St. Boniface Hospital,
Manitoba.

Intra-arterial Thiopentone

SIR,—It has been good to read the report by Professor J. B. Kinmonth and Mr. R. C. Shepherd on experimental work done on intra-arterial injection of thiopentone (*Journal*, November 7, p. 914). The statement that "the danger of ischaemic changes after an intra-arterial injection is greater with strong than with dilute solutions" bears out similar statements made by other writers, and it is disturbing to know that some anaesthetists are still using 5% solution.

A few months ago we pointed out to Messrs. May and Baker Ltd. that their present custom of supplying ampoules containing 1 gramme of thiopentone with only 20 ml. of water is encouraging the continuation of this practice, especially among occasional anaesthetists who will not have other sources of sterile water readily available. We hope that before long all brands of thiopentone will be supplied with sufficient water to make a 2½% solution.—We are, etc.,

DONALD R. KINDSCHI.
GWENDA M. LEWIS.

Christian Medical College and Hospital,
Vellore, South India.

Intravenous Analgesics

SIR,—I read with interest Mr. J. R. Pearson's medical memorandum on the reduction of fractures and dislocations with the use of "pethilorfan" (March 5, p. 706). I used this technique quite extensively in domiciliary treatment of abortions and other obstetrical procedures when I was clinical clerk in the Rotunda Hospital, Dublin. In the majority of cases it did away with the necessity of a general anaesthetic. The dose was 75–100 mg. intravenously, which was given over 30 seconds. This dose varied with age and size of patient. We also found that by this method the patient usually passed into a pleasant sleep and had no real memory of our treatment.—I am, etc.,

Leeds, 6. R. R. MUIR-COCHRANE.

Peak-flow Meter

SIR,—Dr. D. V. Bates (January 2, p. 56) referred to my paper[1] in which I stated: "The measurement of the maximal expiratory flow rate . . . cannot be recommended as a single lung function test." In their letter (March 5, p. 728) Drs. B. M. Wright and C. B. McKerrow suggest that this opinion is probably a consequence of the use of instruments which could not indicate such high flow rates as their peak-flow meter.[2] The statement referred to was based on measurements with Lilly's pneumotachograph and Hadorn's pneumometer; in addition maximal slopes of fast expirations were measured from a spirogram in the same subjects. In 29 normal subjects Lilly's instrument showed peak flows ranging from 144 to 468 litres/min., the pneumometer 180 to 552 litres/min., and the spirogram 222 to 900 litres/min. The latter is comparable to the range of about 200 to over 900 litres/min. found with the peak-flow meter.[2] I agree with Drs. Wright and McKerrow that the Lilly pneumotachograph and the pneumometer probably underestimate the peak flow, and I did mention elsewhere[3] that Lilly's instrument is unsuitable for this purpose.

However, the main reason why the peak-flow measurements were regarded as relatively insensitive as compared to other measures of the speed of maximal expirations was the fact that the values obtained in any one subject were much more variable than the forced expiratory volume ($F.E.V._1$) values. This was true even in well-trained and highly co-operative subjects. Recently this finding has been confirmed by Bovet,[4] in Fleisch's laboratory, who worked with a Fleisch's pneumotachograph with a linear response up to 780 litres/min. Bovet found a coefficient of variation of 4–8% for the peak-flow values compared to 1.5–3.5% for the $F.E.V._1$ values, measured with a spirograph during the same expirations. Bovet writes[4]: "The pneumotachogram of an expiratory fast vital capacity is not very suitable for providing the basis of a physiological test, because its only simply determinable and easily measurable feature—its top—is not easily reproducible in the same subject." If this is true in carefully performed laboratory experiments, even though they have been done on a small scale, it makes one doubt about the practical applications of such a method on a larger scale, where an even larger variability of the measurements is apt to occur. In this respect it is immaterial whether or not the instruments used recorded the highest possible peak flows. Contrary to the suggestion of Drs. Wright and McKerrow that a wide experience on a clinical scale provides better evidence for the value of peak-flow measurements than relatively small-scale laboratory experiments, I submit that such small-scale experiments have provided good evidence, from different sources, that peak-flow measurements are a less consistent characteristic of fast expirations than the $F.E.V._1$. In my opinion this finding is sufficient to prefer the F.E.V. measurements also for clinical purposes. Measurements of the F.E.V. are, after all, also simple to perform, and the instrument recently devised for this purpose by Dr. McKerrow and his associates[5] even improves this simplicity considerably.—I am, etc.,

A. BOUHUYS.

Laboratory of Clinical Physiology,
University Hospital,
Leyden, The Netherlands.

REFERENCES

1 Bouhuys, A., *Acta med. scand.*, 1957, **159**, 91.
2 Wright, B. M., and McKerrow, C. B., *Brit. med. J.*, 1959, **2**, 1041.
3 Bouhuys, A., *Pneumotachografie*. Thesis, Amsterdam, 1956.
4 Bovet, J., *Helv. physiol. pharmacol. Acta*, 1959, **17**, 300.
5 McKerrow, C. B., McDermott, M., and Gilson, J. C., *Lancet*, 1960, **1**, 149.

Blood Carbon-dioxide Tension

SIR,—We would be grateful for the opportunity of discussing some points in connexion with the rebreathing methods for estimating arterial and mixed venous carbon-dioxide tension (pCO_2) which we described in the *Journal* of February 13 (p. 458). A number of people have approached us with the following questions and difficulties:

(1) Is a rapid continuous CO_2 analyser made unnecessary by the simpler procedure? We think not. The methods differ considerably in their applicability. The Collier

method[1] using the rapid analyser gives the answer more quickly and with less need to rely on technique once the instrument is warmed up and calibrated. In addition, a permanent record of the equilibration process can be taken. If the instrument has to be disconnected from its electrical supply between analyses instability during the warming-up period largely loses these advantages. It is the method of choice when the instrument can be kept permanently set up and when speed or the ability to deal with large numbers are important considerations. Thus it is the method of choice for anaesthetic and recovery rooms, respirator units, thoracic surgical units, clinics, and survey work. Our simplified method, having the advantages of extreme portability and analytical simplicity, is preferable for general medical, surgical, and emergency use, but the procedure takes slightly longer, requires greater care, and does not provide a permanent record. As the demand for pCO_2 measurement increases it should surrender some of its present work to the Collier method.

(2) Some people have had difficulty with our simplified method in patients who have small tidal volumes. Whenever we have had the chance to repeat these measurements personally we have overcome these difficulties by attention to the following details. (*a*) Using a mouthpiece and nose-clip rather than a mask whenever possible. This eliminates leaks and reduces dead space to a minimum, enabling smaller bag volumes to be used. As pointed out in our paper, *large* mouthpieces can usually be used even with unconscious and uncooperative patients. (*b*) Attention to the volume of gas in the bag. In the work we described, for the purpose of standardizing our technique we used bag volumes of fixed size. With further experience we now feel that, in routine practice, the aim should be to use the smallest possible bag volume, and it should never be more than twice the tidal volume. This is more easily achieved if a small bag is used. We prefer a bag with an unstretched volume of only 1.5 litres, having a wire cage in the neck to prevent collapse. Larger bags make the tidal volume/bag volume ratio difficult to judge; they make leaks difficult to detect; they tend to collapse at the neck under their own weight unless filled to an undesirably large volume. (*c*) When doubt about the validity of the result remains, the procedure can be modified by prolonging the two rebreathing periods, as described in our paper. This excludes the possibility of clinically important underestimation.

—We are, etc.,

E. J. M. CAMPBELL.
J. B. L. HOWELL.

Department of Medicine,
The Middlesex Hospital,
London, W.1.

REFERENCE

[1] Collier, C. R., *J. appl. Physiol.*, 1956, **9**, 25.

High-pressure Salesmanship

SIR,—My wife and I both being in practice, the flood of circulars from drug firms reached such proportions that we finally decided to try and stop it. Like Dr. R. E. W. Oliver (March 26, p. 963) we too got tired of answering the post at 6.45 a.m. to take in stuff too big for the letter-box.

We had a stroke of good fortune at the start by hearing of the name and address of a medical mailing agency (it had applied to the executive council for an up-to-date nominal roll of doctors), and after a small argument our names were taken off its list. Since then we have written to 47 separate firms. Nine of the first-rank firms sent a courteous acknowledgment and promised to erase our names. One or two made the revealing comment that we should probably get some more letters already in the "pipe-line" before they could be stopped. Five firms had to be written to three times (with letters of increasing acerbity), and four firms twice before they took any notice.

We started this battle in July last and have succeeded in cutting the torrent to a trickle. But we are still at it, as it would appear that new firms spring up and old ones change their mailing agencies.—I am, etc.,

Hastings, Sussex. G. NESBITT WOOD.

SIR,—I think there is a fairly simple answer to the menace of the flood of advertisements that fill our waste-paper baskets each day. All you have to do is to redirect to the sender any unwelcome brochure or pamphlet, adding a note on the envelope: "Please remove my name from your mailing list." A 2d. stamp will suffice in most cases and is cheap at the price.

I have found that this method, which might be called the boomerang, has had gratifying results. I recommend it to fellow-sufferers who wish to obtain relief for themselves and the postman. If widely adopted, it might also convince those drug firms who particularly annoy you (there are some obvious exceptions) that sales resistance is a real thing.—I am, etc.,

Kirkcudbright. D. J. MACMYN.

SIR,—I was glad, as well as interested, to read the letters of Dr. R. E. W. Oliver and Dr. J. E. Morrison on drug-house literature (March 26, p. 963). Though it may seem against our interests, this company has long pointed out that "giant" mailing pieces tend to be disliked, and undue frequency of addressings have been resented.

There is, however, another side. Not all the country's general practitioners will necessarily receive 27 items from the same firm within 77 days. Localized mailings are quite common and it is very possible that Dr. Morrison's part of Scotland was, for a particular reason, mailed intensively by one firm for a short period. It by no means follows that Lancashire received similar treatment at the same time. If it is asked why such tactics are adopted, I am afraid the answer would be that generally speaking they pay, and, whilst individually Dr. Morrison and his colleagues might deny that literature has any effect on them, sales figures for the drugs being promoted show a different answer. It is equally a fact that for every doctor who requests "No more mailing" a letter is received from another doctor, "Please put me on the mailing list."

Even on "giant" mailing pieces there is another side. Professional people, more than any, are unimpressed by the commonplace, and if the advertising departments of pharmaceutical houses, in their efforts to be different, occasionally use excessive sizes, is that necessarily a bad thing? In any case, the more outrageous sizes get short shrift at the hands of postmen, and their perpetrators quickly realize how unwise they are and so revert to more reasonable standards.—I am, etc.,

London, W.5. ALAN G. NICHOLLS,
Managing Director,
The Medical Mailing Co. Ltd.

SIR,—The Minister of Health could help. He should forbid all ordering on E.C.10s of proprietaries except for those made by firms on a special list. To be on the list, a manufacturer would annually have to satisfy the Minister that he was spending (*a*) on advertising (in the widest possible sense) not more than a certain proportion (fixed by the Minister) of his total revenue, and (*b*) on research (excluding "research" by questionary) not less than a certain proportion (fixed by the Minister) of his total revenue. In fixing the proportions

it might be appropriate to use a sliding scale varying with the size of the revenue. This would not only curtail expenditure on advertising, which ultimately comes largely from public funds; it would also drive from the field the purely armchair researcher.—I am, etc.,

West Bromwich. D. SAKLATVALA.

"Imferon"

SIR,—Your leading article entitled "Carcinogenic Risks of Iron-dextran" (March 12, p. 788) was intended to protect patients from "theoretical" risk, and the drastic action taken by the manufacturers must make that effective. Transfusion will often be the alternative treatment. I hope this will not lead to practical danger by imposing a strain on the supplies of blood for transfusion, sufficient to endanger the lives of other patients in an emergency, or to cause danger by stimulating unusual antibodies which may cause difficulty in future emergency transfusions.—I am, etc.,

Preston Hospital, North Shields. CECIL D. JOBLING.

Keats and Anaesthetic Cyanosis

SIR,—I rise at once to Dr. Richard Asher's frivolous suggestion in his first Lettsomian lecture (April 2, p. 985) that Keats must have seen anaesthetic cyanosis. Keats died on February 23, 1821, whereas anaesthesia was first demonstrated successfully on October 16, 1846. But perhaps I am one of the fishes for which this fly was specially cast.—I am, etc.,

Charing Cross Hospital, London, W.C.2. JOHN MILLER.

POINTS FROM LETTERS

Medico-legal Significance of the Fractured Skull

Dr. E. R. D. EASTMAN-NAGLE (Bulwer, Natal, South Africa) writes: Replying to the request of Mr. Desmond Farley (February 13, p. 499), may I suggest the term "brain bruise," with or without fracture of the skull, for the use of the laity (and of the profession as well, maybe)? The adjectival prefix "slight," "severe," or even "fatal" might qualify the phrase, according to the degree of injury.

Hospital Infection and Visitors

Dr. S. W. V. DAVIES (Beacon, Cornwall) writes: Visitors' boils and blains invading our hospitals and clinics (February 20, p. 563) are only one factor in the spread of infection. The more important is the retention of the invaders in the wards. I think that the wool bedding has been condemned in this respect. Wool cannot adequately be sterilized by standard methods, and I suggest that some of the many millions of pounds sterling spent on developing nuclear weapons be diverted to this problem. . . . A radioactive sterilizer for every hospital could eliminate bugs and spores.

Room for the Social Diagnostician

Dr. GARETH R. DAVIES (Wolverhampton) writes: The medical profession as it is organized to-day, in this and other countries, does not yet provide a satisfactory career for the social diagnosticians. The traditional tendency towards brilliant individualism, as opposed to social realism, has made nice niches in the social and medical fabric for certain types of mind only. To-day the sick individual is happily well catered for. However, this is the age when group medicine is returning as the first priority. In the public-health sphere the bacterial problems are increasingly being overcome while the problems of xenophobias, etc., are hardly touched on. The public-health career structure leads essentially to the administrative desk or the university laboratory. It is now time to reorganize the establishment so that the social diagnosticians, whose laboratory is society itself, can pioneer new concepts of social behaviourism.

Obituary

Sir JAMES KILPATRICK, K.B.E., C.B., LL.D., M.B. B.Ch., D.P.H.

Sir James Kilpatrick, dean of the London School of Hygiene and Tropical Medicine, died suddenly in London on April 4 shortly before he was to have delivered a lecture at a London Hospital. He had a distinguished career in the Royal Air Force, retiring as Director-General of R.A.F. Medical Services in 1957. He was 58 years of age.

James MacConnell Kilpatrick was born in Belfast on March 1, 1902. Educated at the Royal Belfast Academical Institution and Queen's University, he graduated M.B., B.Ch., B.A.O. in 1924. In the following year he was commissioned in the Royal Air Force and so began a career which, by the breadth and variation of experience that it embraced, fitted him admirably for the highest position in his service. The first two years he spent as a station or squadron medical officer at various units at home and in India. Then, in 1927, he began a long period of almost four years at the Princess Mary's Royal Air Force Hospital at Halton, where he developed his interest in pathology and public health. In 1931 he was awarded the Arnott Memorial Gold Medal by the Irish Medical Schools and Graduates Association for work at Halton during an outbreak of cerebrospinal meningitis. From Halton he was sent to Iraq, and his overseas experience was later augmented by a war-time tour as principal medical officer, West Africa, and, just before his appointment as Director-General of Medical Services in 1951, a short tour as P.M.O. of the Middle East Air Forces.

[*Elliott and Fry*

Three of his appointments were concerned with research. He spent a year (1936) at the R.A.F. Institute of Pathology and Tropical Medicine, Halton. In the two years up to the outbreak of war he was at the Chemical Defence Experimental Establishment at Porton. He attained air rank as Director of Hygiene and Research in 1947, at a time of the most active growth of the research programme in aviation medicine at Farnborough. More command posts came his way than to the majority of medical officers who achieve high rank. He commanded no fewer than three R.A.F. hospitals—Church Village, Rauceby, and Northallerton. Between these last two posts—from August, 1945, to February, 1946—he completed with distinction the course at the R.A.F. Staff College, Bracknell. This he regarded as a most valuable training. His staff experience included three Air Ministry posts at various stages of his career—M.A.4 in 1939, Director of Hygiene and Research in 1947, and Deputy Director-General in 1950. Appointed O.B.E. in 1946 and C.B. in 1952, he was knighted in 1953. Three years ago he received the honorary degree of LL.D. from his own university. He became Honorary Physician to the King in 1951 and to the Queen from 1952 until his retirement in 1957. He was vice-president of the United Services Section of the Royal Society of Medicine from 1951 to 1957 and president of the Epidemiology and Preventive Medicine Section from 1958 until his death. A member of the Public Health Committee of the B.M.A., he was vice-president of the Section of Preventive and Social Medicine at the Annual Meeting in Edinburgh last year.

He was also a member of the board of governors of University College Hospital.

When he became Director-General in 1951, the youngest man ever to be appointed to that office, there were few facets of Air Force life with which he was not familiar. But breadth of experience alone does not fit a man for the highest posts: personal qualities are what count most of all, and despite a man's achievements it is the personal qualities that are remembered by his friends. The first impression Sir James Kilpatrick left upon people was of kindness and gentleness. As they knew him better they could wonder at his scrupulous fairness, a quality so striking in him that it sometimes reached an almost obsessional degree. He was a serious man, a man for whom his duty came before all else, a man who never spared himself so long as work remained to be done. As a negotiator he was patient, as an innovator moderate but determined; and his ideas and methods did great service to the Royal Air Force at the time of the Waverley Committee, the findings of which were so favourable to the policies he advocated, policies which have contributed much to the stability and efficiency of the medical services.

Lady Kilpatrick, whose maiden name was Marjorie Drean, became his wife in 1928. They had two sons, one of whom is at present serving in the medical branch of the Royal Air Force.

A. B. H. writes: On retirement from the Royal Air Force at the age of 55 Sir James Kilpatrick was invited to become dean of the London School of Hygiene and Tropical Medicine. With his service interests in both tropical and preventive medicine and his desire to continue in active work, he accepted this invitation with particular pride and pleasure. Nevertheless, in passing to so different an environment he sensed that some of his new colleagues in academic life might well fear the "domination" of a director-general. He soon proved to them that they need have no fear. He showed that, as a dean, he fully realized that he was there to encourage and support the academic aims in teaching and research whenever such aims were well thought out and founded, and that, when they were not, it was his job to guide, change, and persuade rather than to rule by order. He rapidly became a popular figure with staff and students alike and took a great deal of trouble to make himself familiar with the problems of both. He also undertook much extraneous public-health and other committee work whenever he believed it was to the good of the School and its tenets that he should do so. Indeed, simple in his tastes and diffident of his powers to the point of shyness, it was always obvious that duty stood out clearly as one of the keywords of his character and life. His early death is a serious loss to the field of public health.

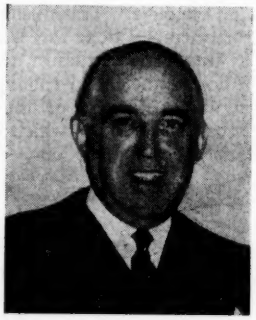
GREGORIO MARAÑÓN, M.D.

Dr. Gregorio Marañón, professor of endocrinology in the University of Madrid, and a leading personality in the literary and medical life of Spain, died in Madrid on March 27, aged 72. He was a Foreign Corresponding Member of the British Medical Association.

Gregorio Marañón was born in Madrid on May 19, 1887, and educated at the College of San Carlos and at the University of Madrid, where he graduated in medicine in 1911. Shortly before this he had been awarded the Martinez de Molina prize by the Madrid Academy, a prize previously won by Ramon y Cajal. Thereafter he studied for a time in Frankfort-on-Main under Ehrlich and then returned to Madrid, where he held numerous appointments, including that of director of the Institute of Experimental Pathology at the General Hospital. At the University of Madrid he first held the chair of pathology and then became professor of endocrinology, a professorship established specially for him.

Professor Marañón was one of the founders of the specialty of endocrinology. His books and papers covered all aspects of the subject, though his main interest was in the sex hormones. His reputation in Spain was such that he was regarded as one of the greatest medical authorities of his time, and he was a former president of the Spanish Academy of Medicine. He travelled widely and was especially well known in South America, where he was often the principal speaker at medical conferences. In 1936 he was elected a Foreign Corresponding Member of the B.M.A. and an Honorary Fellow of the Royal Society of Medicine. A few years ago he visited Britain under the auspices of the British Council, and at about this time also a paper he wrote about the sphenoidal sinus and its value in diagnosis was published in this journal.

Professor Marañón was famous in other spheres besides medicine. A liberal of great influence—and also a personal friend of King Alfonso XIII—he was once described as the midwife of the Spanish Republic, for it was at his house in 1931 that the monarchist leaders arranged for the transfer of power to the Republic. During the Spanish civil war he was at first in the Republican zone of Madrid, and he then left the country, going first to the Argentine and then to Paris. When he returned to Spain in 1942 he abandoned politics, though his signature often appeared on petitions to the Government demanding clemency for political prisoners. An essayist of distinction, he wrote several historical works which brought him right to the forefront of Spanish authors. Using the method of "psychobiography," he was described by a colleague as "un innovador en la enterpretación de los personajes de la comedia humana." Among those whose lives he illuminated were Henry IV of Castille, Count-Duke Olivarez, Antonio Pérez, and Tiberius. This last biography, which he described as a study in resentment, was translated into English in 1956 and received high praise from the critics.



The doors of the faculty of medicine at the University of Madrid were closed in mourning after Professor Marañón's death. He is survived by his widow, one son, who is a lawyer, and three daughters, one of whom is married to Mr. Thomas Burns, of the publishing firm of Burns, Oates and Washbourne.

Dr. PETER BISHOP writes: Don Gregorio was a man of great influence not only in literary and, at one time, in political circles in Spain, but also in medicine. He was certainly a pioneer of endocrinology whose opinion was sought by patients and their relatives not only in Spain but from all over the world. To have been his disciple in itself conferred a certain *cachet* which was much sought after, and he was followed on his rounds by a flock of admiring students, postgraduates, interns, and visitors; and afterwards there might gather in his lecture theatre an audience of up to a hundred of his followers to listen to an address given by some distinguished foreign colleague whom Marañón may have invited to visit him in Madrid or at his country estate near Toledo.

Dr. CHARLES BURNS writes: To have known Dr. Marañón was a great privilege, because it was to know one who was not only a great doctor of medicine and teacher but also a very wise and good man. One of his books was translated into English in 1932, with the title, *The Evolution of Sex*. He wrote many historical-psychological books, as well as textbooks of medicine and endocrinology. This range of output indicates the versatility of his interests and his prodigious capacity for work. He had an intimate knowledge of Spain and its people, of regional cooking, of bull-fighting, and of local geography. In his home he had collected a complete library of books about Spanish travels in all languages. He was beloved by people of all classes and all parties, and his death will be an occasion of national mourning.

D. J. CAMPBELL, F.R.C.P.Ed., D.P.H.

Dr. D. J. Campbell, consultant venereologist for the Sheffield area, died suddenly in the Royal Hospital, Sheffield, on March 6. He was 55 years of age.

Douglas James Campbell was educated at George Watson's College, Edinburgh, and afterwards at the school of medicine of the Royal Colleges in Edinburgh. He qualified in dentistry in 1926 and in medicine in 1927. Finding no true satisfaction in dentistry, he never pursued it, but devoted his energies to medicine. After spending some time in hospital in Edinburgh, first as medical officer in Seafield Hospital and then as house-physician and later house-surgeon in the Royal Infirmary, he worked as clinical assistant and assistant clinical bacteriologist under Mr. David Lees in the venereal diseases department of the Royal Infirmary for three years. During this time he took the D.P.H. and the M.R.C.P. of Edinburgh.

From 1932 until 1937 he was V.D. officer and pathologist to the county borough of Southampton, and consultant in V.D. to the Royal South Hants Hospital, Southampton. In 1937 he was elected to the Fellowship of the Royal College of Physicians of Edinburgh, and from 1937 until 1939 he was V.D. officer and pathologist to the county borough of Grimsby, as well as holding various honorary and consultant appointments to two hospitals in Grimsby and to the City of Lincoln and the Holland county council.

On the outbreak of war Dr. Campbell was commissioned in the R.A.M.C. and served first in Aldershot and later in North Africa, Sicily, Brussels, and Germany. He was promoted to the rank of lieutenant-colonel and was finally adviser in venereology to H.Q. 21st Army Group, B.L.A.

Returning to Grimsby, he resumed his work there until 1949, when he came to Sheffield to take up the appointment of consultant venereologist in the Sheffield area under the N.H.S. He was responsible for supervising V.D. services in a number of hospitals: in the city of Sheffield alone he was consultant venereologist to the Royal Hospital and the Royal Infirmary, as well as to the Jessop Hospital for Women and the City General Hospital. He became an honorary member of the staff of the United Sheffield Hospitals in 1950 and was appointed by the university as part-time lecturer and clinical teacher in venereal diseases.

An enthusiastic member of the B.M.A., Dr. Campbell was chairman of the Grimsby Division in 1948–9, a member of the Central Consultants and Specialists Committee from 1951 to 1958, and he was one of the Sheffield representatives at several Annual Representative Meetings. The author of several papers on subjects connected with his specialty, he was a former president of the Medical Society for the Study of Venereal Diseases.

R. A. T. R. writes: A description of Douglas Campbell's professional activities gives no idea of him as a man. His most striking characteristics were his idealism, the wide range and variety of his outside interests, his warm human sympathies, and his devotion to his family. Having a high regard for the ideals and ethical standards of medicine, he was impatient of those who failed to measure up to them, yet he was kindly and courteous to the junior members of his staff and to his students. For young people, for the physically handicapped, and for children Douglas had a very warm spot in his heart. He worked for the handicapped in the Rotary Club, of which he had been president a few years ago. He had been a Freemason for many years and was an active member of the Church of England.

His skill as a carpenter filled me with envy, and his home contained striking evidence of his handiwork. Walking on the moors, fishing with his sons, gardening and caravanning in the summer, these were all part of his busy life. In his family life Douglas Campbell was particularly fortunate. His charming wife was a wonderful hostess to his guests, and was herself an ex-president of the Inner Wheel.

By his professional colleagues and by his many friends Douglas Campbell will be greatly missed. To his widow and to his two sons we offer our deep sympathy.

D. K. VISWANATHAN, M.B., B.S., D.P.H., M.P.H.

Dr. D. K. Viswanathan, senior regional malaria adviser to the W.H.O. Regional Office for South-east Asia, died on March 27. He was 59 years of age.

Dharmavadani Krishnier Viswanathan was born at Tirunelveli, Madras State, on March 1, 1901. He obtained his medical degrees at the Medical College in Madras in 1923 and his Diploma in Public Health at the same school five years later. In 1937 he was granted the degree of Master of Public Health at the Johns Hopkins School of Hygiene, Baltimore. From 1943 until 1952 he held the post of assistant director of public health with the Government of Bombay State. In 1952 he became director of public health service of the Government of Bombay in charge of public health administration, and held this post until 1956, when he joined the World Health Organization and became senior regional malaria adviser to the Regional Office for South-east Asia. He was a member of the committees of the Indian Council of Medical Research, the Council of Scientific Industrial Research, the W.H.O. Expert Advisory Panel on Malaria, and a Fellow of the Indian Academy of Sciences.

L. J. B.-C. writes: The loss of "D.K.," as Dr. Viswanathan was affectionately called, came as a great shock to all his friends. It is difficult to believe that this unforgettable man, whose boundless energy and brilliant intellect were so widely known, has gone for ever. Malariology has lost in Viswanathan one of its outstanding specialists, a man who has blazed a trail towards malaria eradication in India and in the world. His interest in malariology dates from 1927, when he was assistant medical officer in Madras. In 1935, in the capacity of malaria officer of the Madras Presidency, his was the task of controlling malaria over an area of 142,000 square miles with a population of 47 million. In this he was assisted by one entomologist and by a budget of about $26,000.

The D.D.T. era in India started on July 1, 1945, in Dharwar and Kanara districts of Bombay Presidency at Viswanathan's insistence and thanks to a small supply of the insecticide given by the Army. The success of this first trial was such that by 1949 about 6 million people were under protection in Bombay State. By 1952 over 30 million people were successfully protected from malaria in India, and in 1955 the Indian national malaria control programme came into being, only to be succeeded two years later by the organization of the present national malaria eradication service which, assisted by W.H.O. and I.C.A., protects a population of 390 million.

Although the part played by Viswanathan in the early stages of this programme was limited to Bombay State alone, there is little doubt that D.K.'s experience, drive, and extraordinary talent of persuasion contributed greatly to the success of this largest malaria eradication campaign in the world. His numerous published papers and countless letters and notes are marked by his deep understanding of the epidemiological bases of malaria, by the originality of his approach, and by his facility in expressing his thoughts. His book, *Malaria and its Control in Bombay State*, published in 1950, contains many ideas which were in advance of that time; and his monograph, *Conquest of Malaria in India* (1958), makes delightful reading.

For the past four years he held the post of W.H.O. senior regional malaria adviser responsible for malaria eradication programmes over an enormous area of the South-east Asia Region, where 506 million people were exposed to the disease. He took up and carried on this difficult job with a phenomenal energy and without sparing himself, and his work as an inspired leader, careful guide, and critical judge was outstanding.

Viswanathan had a double personality in which the East and West were extraordinarily blended. He was a western man in his belief in material progress and his respect for Cartesian logic; but he was also (and even more) a devoted Brahmin Hindu, a mystic regarding all earthly phenomena as evanescent and aspiring to the union with the Infinite. A brilliant conversationalist, he was able to quote John Donne and the Bhagavad Gita with equal facility and fervour. Nothing can show his personality better than an extract from his last letter written to some friends in the World Health Organization two weeks before his death:

"The medical pundits have at last declared that my condition is one of myeloma. . . . They are exploring the possibility of my getting treatment by irradiation in India . . . but if it is not available there is no option. . . .

"I have some notes and bits of news on the strategy of eradication of malaria and on our present knowledge of the epidemiology of disappearing malaria It will not be unfitting if I present the Organization with this humble token of my last testament. I can dictate it during those moments that are available between my bouts of pain, prayer, and pethidine. I am able to do this for about one hour every day; I hope to have the notes completed by the end of May, but these 60 minutes a day have to be made up of at least 12 snatches of 5 minutes each, when I am physically able to concentrate my attention.

"Though not over-modest in the past, during the last few years my service with an international organization has taught me a few basic virtues like humility, patience, and human understanding.

"All things must come to an end in this world. I am not worried about it. I have lived well, served well, have a good family, and, above all, excellent comradeship in my official work. So I am quite prepared to meet my Maker."

A kind, loyal, and generous friend, Dr. D. K. Viswanathan is mourned by all who knew him. Our deep sympathy goes to his wife. Rakshmi, and to his son and two daughters.

W. WARD-SMITH, M.D., M.B., F.R.C.S.

Dr. W. Ward-Smith, who practised in Shipley, Yorkshire, died at the Duke of York Home, Bradford, on March 14 at the age of 84 years.

Ward Ward-Smith was born on October 14, 1875. He studied medicine at Edinburgh University, where he was a Grierson bursar and where he graduated M.B., Ch.B. in 1898. He continued his studies at the then Yorkshire College, Leeds, obtaining the F.R.C.S. of England in 1902 and proceeding M.D., with commendation, in 1905. It was while in Leeds that he became friendly with Berkeley Moynihan, whose wife's sister he later married.

Going into general practice in Shipley, near Bradford, he remained there for the rest of his life. It was not long before he was elected honorary consulting surgeon to the Bradford Children's Hospital, a post which he held until the introduction of the N.H.S. in 1948. He held many other appointments, including those of factory surgeon, Post Office surgeon, and surgeon to Sir Titus Salt's Hospital, Shipley. During the first world war he served as a major in the R.A.M.C. A keen member of the B.M.A., he was chairman of the Bradford Division for the session 1937-8. He was particularly gratified when he was made a life member of the Association in 1958 soon after he had retired from active practice. His knowledge of wines was extensive, and when he became president of the Bradford Medico-Chirurgical Society the subject of his presidential address was "A Discourse on Wine."

Well loved and respected, Dr. Ward-Smith had an extensive practice which included a considerable number of the families of business and professional men. He leaves a son and two daughters, and the large gathering of colleagues and former patients at his funeral demonstrated the affection and esteem he had earned.—J. A. P.

FREDERICK GILL, M.D., F.R.C.S.I.

Mr. Frederick Gill, visiting surgeon to Sir Patrick Dun's Hospital, Dublin, and consulting surgeon to the Rotunda Hospital, died at Ballsbridge on March 18.

Frederick Gill was born in Co. Down and graduated in medicine at Trinity College, Dublin, in 1918. Before this he served in the first world war in the Royal Flying Corps, and later, retaining his interest in flying, he took a pilot's licence. In 1921 he proceeded M.D. and was elected a Fellow of the Royal College of Surgeons in Ireland. Not long after qualification Mr. Gill went to Egypt, where he was resident medical officer at the British Hospital at Port Said. On returning to Dublin he joined the staff of Sir Patrick Dun's Hospital and later was appointed assistant to the professor of surgery at Trinity College. In 1946–7 he was president of the Royal College of Surgeons in Ireland.

R. H. M. writes: Gill will be remembered for sound surgery and for sound teaching. He enjoyed teaching, and must have had the pleasure of knowing that he taught well, for both of his two weekly ward-classes were always attended not merely by the students of his own hospital but by those of other hospitals. His out-patient clinics, too, were usually better attended by students than those of other surgeons. His interest in students did not end with the ward or the classroom, for he knew every man on the university XV, and for many years he judged the college races in Trinity Week, "grey topper and all."

Like many surgical teachers he was a general surgeon with some special interests. His colleagues called him in for major injuries, for major abdominal operations, and for major genito-urinary operations, but there was one expanse which he might have claimed as his domain—the surgery of the neck. In his generation he was probably Dublin's leading thyroid surgeon, and continued to lead in this field up to the day of his death. He was one of the first to look for and remove a parathyroid tumour.

Medical Notes in Parliament

CONSULTANTS' MERIT AWARDS

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Lord TAYLOR has been trying to obtain from the Government information about the numbers of consultants in receipt of merit awards, but in two attempts seems not to have got the figures he wanted.

On March 31 he asked for the percentage of consultants employed by boards of governors of teaching hospitals who are in receipt of merit awards, and was told by Lord ST. OSWALD, Lord-in-Waiting, that of the consultants employed by boards of governors 59.3% were in receipt of merit awards; and that consultants also employed by regional hospital boards were included in this figure.

Lord TAYLOR also asked for the percentage of consultants employed by regional hospital boards in receipt of merit awards. Lord ST. OSWALD stated that of the consultants employed by regional hospital boards 30.9% were in receipt of merit awards; and that consultants also employed by boards of governors were included in this figure.

If at First You Don't Succeed . . .

Lord TAYLOR, who had expressed some perplexity about these figures, renewed his inquiries on April 5, this time asking for the percentage of (*a*) consultants, and (*b*) consultants aged 50 or more, employed by boards of governors of teaching hospitals who were in receipt of A and B merit awards. Lord ST. OSWALD told him that of

consultants employed by boards of governors 33.5% were in receipt of A and B merit awards, adding again that consultants also employed by regional hospital boards were included. The information asked for in the second part of Lord Taylor's question was not available.

Lord TAYLOR asked to be given the information he sought without the inclusion of consultants and others employed by regional hospital boards, which confused the figure at which he was trying to arrive. Lord ST. OSWALD replied that as he understood it Lord Taylor asked for an overall figure. That figure was 33.5%. That was the true figure in respect of consultants employed by boards of governors. To subtract from that the proportion of consultants employed by boards of governors but also employed by regional boards would not be a true figure according to Lord Taylor's questions. Lord TAYLOR said that Lord St. Oswald had got it muddled again. He was including persons employed as consultants by regional boards who were employed as registrars or in other capacities by boards of governors. A little calculation based on the report of the Royal Commission would show that the answer he required was 40%, and that the answer which Lord St. Oswald was unable to give was 83%. Lord ST. OSWALD said he would not say that Lord Taylor was muddled, but he was mistaken. The subtraction could be done in relation to the first two answers given to Lord Taylor; the overall figure then given was 59.3%, and, subtracting from that the proportion of consultants with merit awards employed both by boards of governors and regional boards, the figure was 50%.

Lord TAYLOR: I am very interested because I believe the figure to be 80%.

Lord ST. OSWALD added another calculation: the overall figure for consultants employed by regional boards was 30.9%; subtracting the proportion of consultants employed both by regional boards and boards of governors, the figure became 24%.

Lord TAYLOR: I believe the last figure is correct.

Lord ST. OSWALD: I am delighted to hear it, but I believe Lord Taylor will find that both figures are correct.

1959 Awards

Mr. L. PAVITT (Willesden, West, Lab.) asked the Minister of Health in the Commons on April 4 to state the number of distinction awards given to consultants for the year 1959, and to give a table showing the specialties of the consultants receiving them.

Mr. D. WALKER-SMITH told him the number was 216, divided by specialties as follows: general medicine, 42; diseases of the chest, 7; mental health, 13; neurology, 2; paediatrics, 8; radiology, 5; radiotherapy, 1; pathology, 16; dermatology, 5; ophthalmology, 4; general surgery, 36; anaesthetics, 16; neurosurgery, 10; plastic surgery, 4; thoracic surgery, 4; orthopaedic surgery, 11; dentistry, 8; ear, nose, and throat, 3; and obstetrics and gynaecology, 21.

Mr. PAVITT asked when the last review was made for the merit awards to consultants in connexion with the Central Middlesex Hospital. Mr. WALKER-SMITH stated that eligible consultants in all hospitals were reviewed annually. The 1959 review was completed recently.

QUESTIONS IN THE COMMONS

Costs and the Legal Aid Scheme

Mr. W. WELLS (Walsall, North, Lab.) asked the Attorney-General on April 5 whether he would consider incorporating in the Legal Aid Scheme provision for payment of the taxed costs, in whole or in part, if the court so ordered, of parties who, not themselves having a civil aid certificate, had successfully contested proceeding against assisted persons. Captain J. LITCHFIELD (Chelsea, Con.) asked the Attorney-General if he was aware of the continuing injustice of the present arrangement as to costs under the Legal Aid Scheme, whereby defendants could be compelled to pay the costs of plaintiffs who had been assisted under the Scheme, but were unable to recover any costs from such plaintiffs in cases where judgment was given against such plaintiffs; and if he would introduce legislation to correct this anomaly.

Sir JOCELYN SIMON, the Solicitor-General, said the problem of recovering costs from an impecunious litigant, whether or not he was an assisted person, was inherent in our legal system. The Legal Aid and Advice Act already provided payment by the assisted litigant of the costs of a successful opponent up to the amount whch the court considered it is reasonable for him to pay. There were serious objections to all the alternatives so far suggested, and he could not therefore hold out any hope of legislation amending the Legal Aid Scheme in this respect.

Mr. WELLS suggested that the Attorney-General should seriously consider the possibility of providing assistance from public funds in certain of these cases, particularly in view of the embarrassment which the absence of such arrangements frequently occasioned to persons in the position of trustees. The SOLICITOR-GENERAL: No, Sir. We discussed the matter on the second reading of the Legal Aid Bill, and I then ventured to suggest some of the serious objections to that proposal.

Captain LITCHFIELD asked if the Minister was not aware that very heavy losses were incurred by innocent persons under the present system. Did he not agree that this was a case of "Heads I win, tails you lose" for assisted persons, and did he really think it acceptable that this anomaly should be allowed to continue? The SOLICITOR-GENERAL replied that the safeguard was in the screening of the case initially by the Legal Aid district and area committees.

Expenditure on Hospital Building

Mr. WILLIAM SHEPHERD (Cheadle, Con.) asked the Minister of Health on April 4 if he would state the estimated value of new hospital building in the years 1935–9 and 1954–8 expressed in 1935–9 prices; and if he would express both the figures as a percentage of the national income. Mr. WALKER-SMITH stated that the figures available for 1935–9 did not permit of accurate computation and comparison, but the best estimates that could be made suggested that hospital capital expenditure for the four corresponding financial years was of the order of £32m., or about 0.17% of the national income at the time. The most nearly comparable figures for 1954–5 to 1957–8 were of the order of £57m., and were estimated at about £16m. at the prices ruling in the earlier period and about 0.09% respectively.

G.P. Appointments Systems

Mr. PAVITT asked the Minister to what extent he had considered the organization of an appointments system by a general practitioner within the Health Service which would merit distinction and thus be considered in relation to any rearrangement of the distribution of the central pool. Mr. WALKER-SMITH said he was aware that an increasing number of doctors had an appointments system which, where practicable, had obvious advantages. It would not be appropriate for him to comment at the moment on the distribution of the central pool.

U.K. Contribution to W.H.O.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) asked the Minister whether he would increase the United Kingdom contribution of £431,500 to the World Health Organization, having regard to the high incidence of disease, including malaria, in many countries for which the United Kingdom had responsibilities. Mr. WALKER-SMITH replied that the United Kingdom contributions to the World Health Organization's regular budget were assessed annually by the World Health Assembly, and had increased by almost 50% between 1950 and 1960. The proposed budget for 1961 foreshadowed a further increase of about 10% over 1960.

"Flying Doctor" Service in Africa

Dr. SUMMERSKILL asked on April 5 what progress had been made in establishing a flying-doctor service in the

African territories where there was a special need for an emergency medical service. Mr. C. J. M. ALPORT, Minister of State for Commonwealth Relations, said that arrangements were being made for a survey party of the "Flying Doctor Service of Africa" organization to visit Northern Nigeria, Kenya, and Tanganyika to discuss with the governments concerned the possibility of establishing flying-doctor services in their territories. Dr. SUMMERSKILL asked if they were co-operating with the Australian service, which had been so successful. Mr. ALPORT said he did not know whether there was direct co-operation, but the proposed scheme, which had a romantic background, was based on the experience gained in Australia in operating a service of this sort.

V.H.F. Radiation Hazards

Mr. ROY MASON (Barnsley, Lab.) asked the Postmaster-General on April 6 what were the conclusions of the expert committee which had considered the hazards associated with radio-radiation from high-powered, very-high-frequency transmitters, including forward scatter and radar stations. Mr. J. R. BEVINS told him that the committee had now recommended certain precautions to be taken at establishments where such radiation might be generated. He was arranging for the recommendations to be published in booklet form by the Stationery Office.

Salary Differentials of University Teachers

Mrs. JUDITH HART (Lanark, Lab.) asked the Chancellor of the Exchequer on April 7 if he was aware of the representations of the Association of University Teachers, as expressed to the University Grants Committee, that no new proposals concerning the salaries of university teachers should include further differentials beyond those at present existing between teachers of medical and non-medical subjects; and what action he proposed to take.

Sir EDWARD BOYLE, Financial Secretary, stated that the Chancellor was aware of these representations. He was at present considering the advice which he had received from the University Grants Committee on university academic salaries generally, and he had no statement to make.

Medico-Legal

COMPULSORY TREATMENT

[FROM OUR LEGAL CORRESPONDENT]

On February 4 the Oxford magistrates ordered that a woman with chronic pulmonary tuberculosis should be removed to the Osler Hospital for three months (*The Times*, February 5).

The magistrates order was made on the application of the Oxford City Council under Section 172 of the Public Health Act, 1936. That section empowers magistrates to order the removal of a person suffering from tuberculosis of the respiratory tract to a hospital or institution and to order his detention and maintenance there for not more than three months. Such an order can only be made if the magistrates are satisfied that the patient is in an infectious state, that his circumstances are such that proper precautions to prevent the spread of infection cannot be taken or are not being taken, that serious risk of infection is caused to other persons, and that accommodation is available in a suitable hospital vested in the Minister of Health. The order may be continued for further periods of three months on further application to the magistrates. The county council or local authority making any application under this section may be ordered by the magistrates to make a contribution towards the maintenance of the patient's dependants.

In the present cases evidence was given that the woman in question had been suffering from pulmonary tuberculosis for twelve years, that vain efforts had been made since 1948 to get her into hospital, and that she was infectious.

Where Powers Exist

In general one has the privilege of being ill, or dying, without resorting to medical treatment if one wishes (although criminal liability might arise if one compelled one's children to exercise this privilege). The Public Health Act, 1936, makes some exceptions to this general rule, in order to reduce the spread of infection of a limited class of diseases: Section 172 refers to tuberculosis of the respiratory tract only; Section 169 makes similar provisions regarding "notifiable diseases." Under Section 169 a justice of the peace can make an order for the removal to hospital of a person suffering from a notifiable disease on proof of the same matters as are required by Section 172. But curiously Section 169, unlike Section 172, makes no provision to enable the magistrate on the first application to order the patient's *detention* in the hospital, so that the patient may submit to the removal and then immediately return home; and if he were prevented from returning he would have a cause of action for false imprisonment. An order for such a patient's detention can be made only after he has become an inmate of a hospital, on proof that he has no suitable lodgings to which he can return where the spread of infection will be prevented (Section 170). Any compulsory detention made before the date of such order is made at risk of a civil action for false imprisonment. A detention order made under Section 170 may be for any period: there is no three months' limit. The differences between these provisions and those relating to tuberculosis spring from the fact that they originated in different statutes codified in the Public Health Act.

Similar provisions are made for London in the Public Health (London) Act, 1936.

DUTY TO PROTECT HEALTH OF NURSES

[FROM OUR LEGAL CORRESPONDENT]

A male nurse, Joseph Sorman, aged 42, of Slamannan, Stirlingshire, was on February 12 awarded £5,000 damages in the Court of Session against his employers in respect of tuberculosis contracted as a result of their negligence. His employers were the board of management of the Royal Scottish National Institution, Larbert (*Glasgow Herald*, February 13). Mr. Sorman's case was that he contracted the disease as a result of personal contact while nursing mental defectives suffering from various diseases including tuberculosis, and that the hospital had not taken reasonable care to safeguard his health.

The court found that in 1947 Mr. Sorman was *x*-rayed and found to be clear of tuberculosis: it inferred that on entering the hospital's employment in October, 1948, he was not suffering from the disease. But in 1951, mass radiography of the staff and patients of the hospital showed that he was then suffering from the disease: from that date the disease progressed intermittently until Mr. Sorman was incapacitated in 1956. Owing to delay in treatment full recovery was not possible.

The court held that it was the plain duty of the hospital board to take reasonable care to safeguard the health of Mr. Sorman in view of the risks of his employment. However, although Mr. Sorman had been examined from time to time his case history had never been considered as a whole by a specialist competent to advise him. Mr. Sorman's disability was the result of the negligent failure of the board to keep themselves informed of his state of health and to take reasonable precautions.

CORONERS' CASES

Hospital Ruling Criticized

The coroner for the Forest of Dean expressed his disapproval of an order banning the use of cot-sides for

keeping elderly patients in bed which, he was told, had been given at the Mitcheldean Hospital. He was holding an inquest on Mrs. Elizabeth Price, aged 80, and a verdict that death was due to heart failure was recorded. Whilst she was a patient in the hospital Mrs. Price fell out of bed twice on the night of February 19. On the second occasion she sustained a lacerated scalp, necessitating three stitches, and a black eye. She died eleven days later on March 1.

A medical officer to the hospital said that the falls did not contribute to her death. On the suggestion of a geriatric consultant the cot-sides had been removed so that the old people should not feel restricted. The night nurse said in evidence that instructions had been given that the cot-sides were not to be used. The coroner, Mr. M. F. Carter, said it was deplorable that such a state of affairs should exist, and added that he hoped a clearer order would be given that cot-sides must be available for use if the condition of any patient demanded them. He attached no blame to the matron or the staff, but expressed his regret that they had to carry out such an order (*Western Mail*, March 4).

Haemopericardium after Intracardiac Injection

A newborn baby with erythroblastosis was having an exchange transfusion in the first few hours of life. Because of her very weak condition it became necessary to administer an intracardiac injection. Despite every attempt to save the baby's life she died.

Dr. R. E. Potts, pathologist at Middlesbrough General Hospital, found that the needle used for the intracardiac injection had penetrated a vein on the anterior surface of the heart. This had resulted in a haemopericardium. The pathologist said in evidence that this was an extremely rare complication which had never occurred in his own previous experience. The coroner, Mr. Arthur Knott, said that the injection was a necessary one in the circumstances and recorded a verdict of misadventure (*The Journal*, March 16).

Vital Statistics

Census, 1961

Next year's Census will take place on Sunday, April 23. It will be the sixteenth nation-wide census to be held in Britain, the first having been in 1801. Because electronic equipment will be used to "process" the results it is probable that the findings will be published sooner than after the 1951 Census. Some of the questions will not be asked of the whole population but will be put to a 10% sample. New information to be gathered will provide information about the number of people with qualifications in science or technology and about the jobs they are doing. —*Draft Statutory Instruments: The Census Order, 1960.*

Population Forecasts

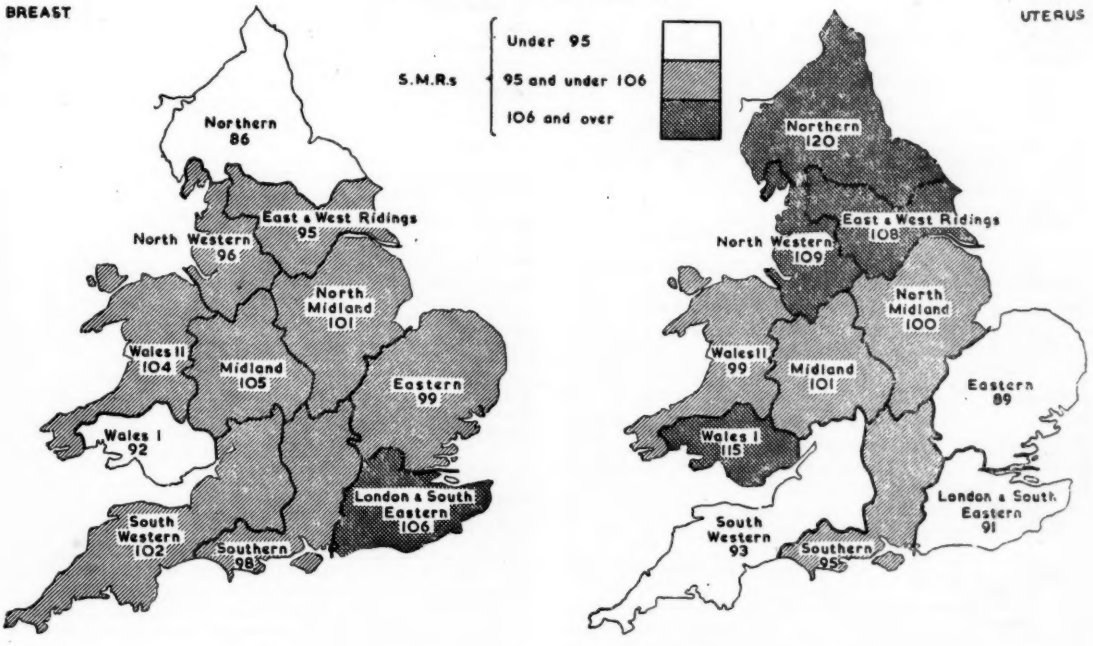
The estimated population of England and Wales in mid-1959 was 45,504,000. If projections of the population based on certain assumptions are made, this figure will rise to 46,468,000 in 1964, to 49,230,000 in 1979, and to 52,384,000 in 1999. These projections show that the excess of 1,500,000 females in 1959 would decrease gradually until in 1999 there were only 512,000 more females than males. At present the proportion of the population of pensionable age (males 65 and over, females 60 and over) is 14.7%. This will increase to 17.9% in 1989, and then decline slightly to 16.7% in 1999.—*The Registrar-General's Quarterly Return for England and Wales, 4th Quarter, 1959.*

Cancer of Uterus and Breast

The maps reproduced here show the variations in the standardized mortality ratios (England and Wales, 100) for cancer of the uterus and female breast in 1955–7. For cancer of the breast the ratios were lowest in south-east

Standardised Mortality Ratios for cancer of the uterus and female breast, 1955-57

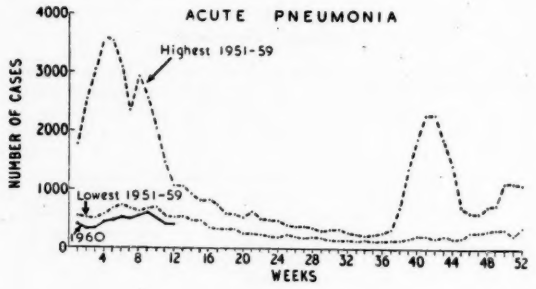
Standard regions of England and Wales

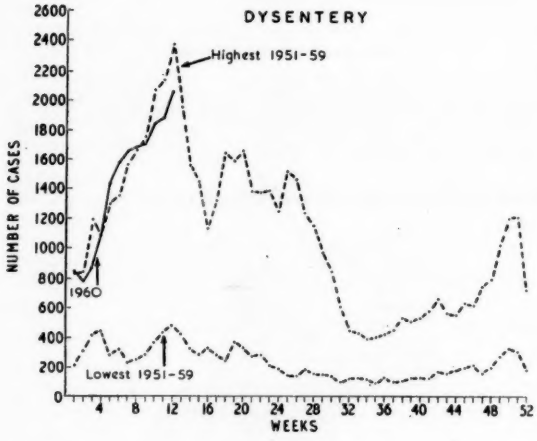


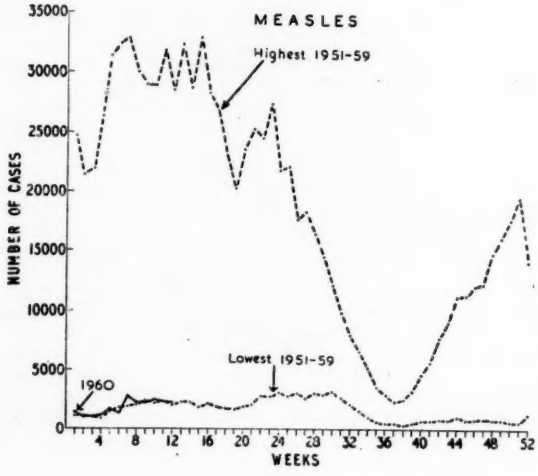
Wales and in the northern region and highest in the London and south-eastern region. On the other hand, for cancer of the uterus the ratios were lowest in the London and south-eastern region and highest in south-east Wales and the northern region.—*The Registrar-General's Quarterly Return for England and Wales, 4th Quarter, 1959.*

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 26** (No. 12) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	1	0	3	0	3	2	0	1	0	
Dysentery ..	2,067	257	185	20	7	1,005	137	112	14	4
Encephalitis, acute	0	0	0	0		2	0		0	
Enteric fever:										
Typhoid ..	1	1	0	0		0	0	0	0	1
Paratyphoid ..	2	0	2	0	1	16	1	1 (B)	0	
Food-poisoning ..	217	26	10	0		109	11	4	0	
Infective enteritis or diarrhoea under 2 years				13	20				8	15
Measles*	2,198	83	102	4	29	19,526	1360	737	467	514
Meningococcal infection	21	4	16	1	1	21	2	7	0	1
Ophthalmia neonatorum .. .	26	3	3	0		17	1	2	0	
Pneumonia† ..	418	17	180	18	5	869	33	311	46	8
Poliomyelitis, acute:										
Paralytic ..	2	0	0	} 0	1	{ 14	3	1	} 0	
Non-paralytic ..	2	1	0			4	0	0		
Puerperal fever§ ..	178	37	10	1	1	158	15	8	1	
Scarlet fever ..	1,152	43	87	23	29	996	73	59	29	12
Tuberculosis:										
Respiratory ..	419	48	54	9		646	47	80	19	
Non-respiratory	50	3	10	3		45	8	7	6	
Whooping-cough	903	63	186	4	25	499	21	34	44	115

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	1	0		0		1	1		0	
Encephalitis, acute		1			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	0	0	0	6	0	1	1	0
Influenza	36	2	0	0	2	421	10	13	9	3
Measles	0	0	0	0	0		0	0	0	0
Meningococcal infection		0	0				1	1		
Pneumonia ..	630	48	30	21	9	954	55	47	38	27
Poliomyelitis, acute	0	0		0	0	3	1		0	0
Scarlet fever ..	0	0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	} 69	{ 2	2	2	4	} 101	{ 4	7	1	2
Non-respiratory		1	0	0	0		2	2	0	1
Whooping-cough	2	0	0	0	0	1	1	0	0	1
Deaths 0–1 year ..	329	29	31	8	11	321	30	36	11	16
Deaths (excluding stillbirths) ..	10,750	821	603	151	193	11,567	749	710	175	213
LIVE BIRTHS ..	16,254	1323	1063	320	404	13,811	1206	975	320	405
STILLBIRTHS ..	314	16	25			304	24	18		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Feeding Antibiotics to Farm Animals

The Agricultural and Medical Research Councils have set up a joint committee to examine the possible consequences of feeding antibiotics to farm animals and to consider whether this practice endangers human or animal health. Professor A. A. MILES, director of the Lister Institute of Preventive Medicine, is chairman of a scientific subcommittee which will examine the evidence in detail and place its findings before the main committee.

Meals in Hospitals

The Nuffield Provincial Hospitals Trust has made a grant of £27,500 to the London School of Hygiene and Tropical Medicine for the purpose of a scientific study of the nutritive value of meals provided in hospitals.

The medically qualified members of the advisory committee so far include Professor D. D. REID (professor of epidemiology, London School of Hygiene and Tropical Medicine), Professor R. A. MORTON (professor of biochemistry, University of Liverpool) and Dr. F. AVERY JONES (chairman of the Hospital Catering and Diet Committee of King Edward's Hospital Fund for London). The study will be directed by Professor B. S. PLATT, and is a result of a nutritional survey made by a small team under his direction in a number of hospitals in Cornwall. The conclusions of the limited study were such as to persuade the trustees that the general subject was of importance and warranted a country-wide investigation. One of the advisory committee's first tasks will be to decide upon the sample of hospitals to be included.

International Federation of Surgical Colleges

A meeting of the executive committee of the International Federation of Surgical Colleges was held recently in Utrecht, with the president, Sir HARRY PLATT, in the chair.

It was reported that the Federation had been admitted into official relations with the World Health Organization, and Sir Harry Platt was appointed as its representative to the Thirteenth World Health Assembly in Geneva in May, 1960. The committee received reports on the progress of its working parties on surgical missions, the training of surgeons, and the interchange of young surgeons between different countries. Arrangements were announced for the 1960 meeting of the Federation, which is to be held in the Royal College of Surgeons of England on October 18–20. The theme of the meeting is to be "The Training of Surgeons," and the other colleges contributing to the programme will be the Royal College of Surgeons of Edinburgh, the Royal College of Surgeons in Ireland, the Royal Faculty of Physicians and Surgeons of Glasgow, and the American College of Surgeons.

The Fireman's Health

A recently published booklet, *Health and the Fireman*, draws attention to the health hazards of fire-fighters and to the lack of knowledge—and, therefore, the need for research—on certain aspects of these hazards.

The Registrar-General's 10-yearly occupational analysis of deaths, for instance, includes firemen with policemen, so that it is difficult to tell if in fact they are more prone than others to certain diseases; also, very few, if any, studies have been carried out on the effects of heat on firemen at fires. "No unit of the Army would enter battle without a medical officer. . . . Surely it is now time that consideration was given to the appointment of at least one medical officer to study the problems discussed in this booklet," concludes the author, Dr. M. D. WARREN. The publishers are Hodgetts, Ltd., 72–78, Fleet Street, London, E.C.4, and the booklet costs 1s. 6d.

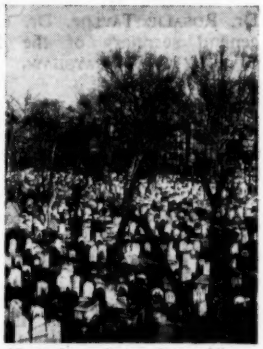
British Diabetic Association

At a meeting at Guy's Hospital on April 1 a Medical and Scientific Section of the British Diabetic Association was formally constituted. Professor F. G. YOUNG, F.R.S., was elected as chairman, and Dr. J. M. STOWERS (Dundee) and Dr. D. A. PYKE (London) as honorary secretaries. Inquiries concerning membership should be addressed to the British Diabetic Association, 152, Harley Street, London, W.1.

Bunhill Fields

London's City Corporation is seeking powers to turn part of Bunhill Fields, the dissenters' burial ground in Finsbury where lie Bunyan, Defoe, and Blake, into a public garden.

There are more doctors of divinity buried there than doctors of medicine, though there is a memorial to one doctor—NATHANIEL UPTON—who was very active during the plague year and survived it to die in 1696. A good patient is commemorated (Dame MARY PAGE, who died, aged 56, in 1728: "In 67 months she was tap'd 66 times, Had taken away 240 gallons of water, Without ever repining at her case, Or ever fearing the operation"), and a treasurer of St. Thomas's Hospital, Captain JOHN SMITH, who died in 1698. There, too, lies the Rev. JOHN TOWNSHEND—a comparative newcomer to the Fields in 1826—who was so horrified by the plight of the deaf and dumb that he founded the London asylum for the deaf and dumb in Bermondsey. Tradition holds that Bunhill Fields, which held 124,000 when it was closed in 1852, is the site of a Saxon burial ground, and it is suggested that it owes its name, a corruption of Bone Hill, to the 1,000 cartloads of bones which were said to have been removed there from the charnel of St. Paul's Cathedral in 1549.



[*Radio Times Hulton Picture Library*

Permanent Secretary, Ministry of Health

Sir JOHN HAWTON has relinquished his appointment as Permanent Secretary of the Ministry of Health, and Mr. B. D. FRASER, at present a deputy secretary in the Ministry of Civil Aviation, has been appointed to succeed him.

Department of Health for Scotland

Dr. W. D. HOOD has been appointed deputy chief medical officer in the Department of Health for Scotland in succession to Dr. R. J. PETERS, who is retiring.

Scottish Regional Hospital Boards

The following are among those reappointed or appointed to serve as members of regional hospital boards in Scotland from April 1:

Northern: Dr. J. RONALD, Dr. M. M. WHITTET. *North-eastern:* Mr. E. G. COLLINS, Professor J. CRAIG. *Eastern:* Professor G. H. BELL. *South-eastern:* Dr. A. G. CRUIKSHANK.* *Western:* Dr. R. BLACK,* Dr. J. C. J. IVES, Dr. D. MCKAY HART.* (*New appointments.)

"Family Doctor"

The April issue of *Family Doctor* is now available, price 1s. 6d. It contains a symposium on road safety which includes articles by Mr. W. GISSANE on road-traffic accidents, Mr. J. D. M. CARDELL on drivers' eyesight, and Dr. A. LEITCH on driving and personality.

Hunterian Society Competition

The subject for the Hunterian Society's 1960 Gold Medal Essay Competition is "The Management of Chronic Arthritis in General Practice." The competition is open to all general practitioners resident within the British Commonwealth. Details may be obtained from the Hon. Secretary, Mr. G. QVIST, 72, Harley Street, London, W.1.

Civil Defence

New regulations recently approved by both Houses of Parliament oblige local authorities to make plans for the prevention and control of disease arising out of hostile action or its threat when required to do so by the Minister of Health. (Civil Defence (Disease) Regulations, 1960.)

Cars for Disabled

The Minister of Health, Mr. WALKER-SMITH, has announced that small cars are to be provided for those disabled war pensioners who are eligible for Government power-propelled tricycles. It will be some months before

the issue can start—to the most seriously disabled first—and about two years before all the cars needed can be supplied, so tricycle owners are asked to wait until the Ministry informs them that an exchange is possible.

"Getting Married, 1960"

The *Family Doctor* booklet, *Getting Married, 1960*, is now available at 1s. a copy. Many aspects of the topic are discussed by, among others, Dr. DORIS ODLUM and Dr. ROSALIE TAYLOR, Dr. LESLIE WEATHERHEAD, and the general secretary of the National Marriage Guidance Council, Mr. J. BRAYSHAW.

People in the News

Dr. R. W. GILLIATT, assistant physician at the National Hospital for Nervous Diseases, is to be best man at the wedding of Princess Margaret and Mr. Antony Armstrong-Jones.

Dr. T. STAPLETON, assistant director of the paediatric unit, St. Mary's Hospital Medical School, has been appointed professor of child health in the University of Sydney and director of the Institute of Child Health there from July 1.

COMING EVENTS

Postgraduate Course in Industrial Health.—Durham University, April 28–June 16. Details from Professor R. C. BROWNE, Nuffield Department of Industrial Health, the Medical School, King's College, Durham University.

Royal College of Surgeons in Ireland. — London Association: Annual dinner and dance, the Rembrandt Hotel, Knightsbridge, London, S.W.1, April 28. Details from Dr. D. S. MAGNER, 56, Glenister Park Road, London, S.W.16.

Kensington and Hammersmith Division, B.M.A.—This Division, in co-operation with the West London Faculty of the College of General Practitioners, is relaying a series of colour television demonstrations from the British Postgraduate Medical School and Hammersmith Hospital to the audience in the Royal College of Surgeons in May, 1960. Admission by ticket. Details from Dr. J. D. W. WHITNEY, 60, Hilary Road, Shepherd's Bush, London, W.12.

T.A. Medical Officers' Association.—Annual dinner: Headquarters Mess, R.A.M.C., Millbank, London, May 13, 7.30 p.m. Details from the Honorary Secretary, Colonel J. A. DUDGEON, 41, Flood Street, London, S.W.3.

Chest and Heart Association.—Symposium: "Current Trends in Cardiology," June 8, Barnes Hall, Royal Society of Medicine, 1, Wimpole Street, London, W.1. Details from the Chest and Heart Association, Tavistock House North, Tavistock Square, London, W.C.1.

Dinghy Meeting.—A dinghy meeting, using G.P. 14's, has been arranged at the Northampton Sailing Club on June 9. All medical men are invited, and particulars can be had from Mr. G. C. SAWYER, 23, de Montfort Street, Leicester.

5th International Congress of Gerontology.—Sponsored by the International Association of Gerontology: San Francisco, August 7–12. Details from Dr. LOUIS KUPLAN, Post Office Box 2103, Sacramento, 10, California, U.S.A.

6th Pan-American Congress of Pediatrics.—Caracas, Venezuela, August 7–13. Details from the Secretariat, Congreso de Pediatria 1960, Apartado Postal 3122, Caracas, Venezuela.

11th International Astronautical Congress.—Royal Institute of Technology, Stockholm, August 15–20. Papers on physiological and psychological aspects of life in extraterrestrial environments will be included. Details from Swedish Interplanetary Society, IAF–60, Box 5045, Stockholm, 5, Sweden.

6th International Congress of Internal Medicine.—Basle, August 24–27. Details from the secretariat of the Congress, 13, Steinentorstrasse, Basle, Switzerland.

2nd International Course of Lyophilization.—Institut National des Sciences Appliquées, Lyons, France, August 29 to September 9. Opening lecture by Dr. A. S. PARKES, F.R.S.: "Lyophilization in Biology and Medicine." Details from Dr. LOUIS R. REY, Laboratoire de Physiologie, École Normale Supérieure, 24, Rue Lhomond, Paris, 5, France.

8th World Congress of International Society for Welfare of Cripples.—New York, August 29 to September 3, 1960. Details of Congress and of International Rehabilitation Film Awards from the Central Council for the Care of Cripples, 34, Eccleston Square, London, S.W.1.

5th International Congress on Nutrition.—Washington, D.C., September 1–7. Chairman of organizing committee: Dr. PAUL GYÖRGY, professor of paediatrics, University of Pennsylvania. Details from Dr. MILTON O. LEE, general secretary, 9650, Wisconsin Avenue, Washington, 14, D.C., U.S.A.

6th International Congress of Microbiological Standardization.—Wiesbaden, Germany, September 5–10. General reports will include one on the production, control, and application of live polio vaccines. Details from Postfach 167, Interstandard Congress, Marburg, Lahn, Germany.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Tuesday, April 19

ILFORD MEDICAL SOCIETY.—At King George Hospital, Ilford, 8.45 p.m. Dr. I. D. Wilson: Words Without End.

Wednesday, April 20

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. M. T. Morgan: Economics of Local Authority Pest Control (illustrated).

●SOCIETY OF APOTHECARIES: FACULTY OF THE HISTORY OF MEDICINE AND PHARMACY.—5.30 p.m., Gideon Delaune Lecture by Sir John Charles: Roger Bacon on the Errors of Physicians.

Thursday, April 21

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—4.15 p.m., Arnott Demonstration by Dr. B. D. Wyke Human Cerebral Circulation.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., papers by Dr. J. D. Fulton, Dr C. S. Leithead, Dr. W. E. Ormerod, and Professor A. W. Woodruff and Dr Stanley S. Bell.

Friday, April 22

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor K. Bloor: Natural History of Arteriosclerosis of the Lower Extremity.

Saturday, April 23

NORTH-EAST METROPOLITAN THORACIC SOCIETY.—At Lecture Theatre, Department for Research in Industrial Medicine, London Hospital, E., 10.30 for 11 a.m., Dr. A. I. G. McLaughlin: Diagnosis of the Pneumoconioses, with Special Reference to *X*-ray Films and Classification.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Guest.—On March 29, 1960, at Dar es Salaam, Tanganyika, to Ilse, wife of Dr. J. G. Guest, a son—Richard Malcolm.

DEATHS

Connell.—On March 24, 1960, at Abberton, Worcs, John Stewart Marshall Connell, F.R.C.S.Ed., L.D.S., late of Birmingham.

Baker.—On March 20, 1960, at Ardvar, Adelaide Road, Walton-on-Thames, Surrey, Martyn Wilfred Baker, M.B., B.Ch.

Feeny.—On March 24, 1960, at 342, Stockport Road, Longsight, Manchester, Patrick Joseph Feeny, M.B., B.Ch.

Foulkes.—On March 22, 1960, at The Homestead, Station Road, Sidmouth, Devon, Peter Gifford Foulkes, M.B., B.S., late of King's Lynn, Norfolk, aged 81.

Heaton.—On March 21, 1960, in Canada, Charles Howard Heaton, O.B.E., M.B., Ch.B., Commander, R.N., retired, late of Birmingham, Warwicks.

Howett.—On March 19, 1960, the result of an accident, Robert Anthony Howett, M.B., F.R.C.S., of Edinburgh, formerly of Melbourne, Australia, aged 31.

Hughes.—On March 23, 1960, in King's College Hospital, London, S.E., Daniel Hughes, M.B., B.Ch., D.P.H., of 74, Camberwell Grove, and 14, Honor Oak Rise, London, S.E.

Macdonald.—On March 22, 1960, at Keyworth, Lundin Links, Fife, George Macdonald, M.B., Ch.B., D.P.H.

MacDougall.—On February 5, 1960, Allan Alexander MacDougall, L.R.C.P.&S.Ed., L.R.F.P.S., of 10, Cecil Street, Glasgow, W.

Minett.—On March 16, 1960, at Langham Nursing Home, Oakham, Rutland, Ethel Mary Minett, M.D., D.P.H., late of Hong Kong and Madeira, aged 72.

O'Loughlin.—On March 23, 1960, Herbert John O'Loughlin, M.B., Ch.B., D.P.M., of Oulton Hall, Oulton, near Leeds, Yorks.

Scott.—On March 17, 1960, at his home, Jersey, Channel Islands, John Scott, D.S.O., O.B.E., M.B., F.R.C.S.Ed., D.P.H., Colonel, I.M.S., retired.

Wilcox.—On March 22, 1960, at Shetland, David Cooper Main Wilcox, M.B., Ch.B., D.A., of 14, Learmonth Gardens, Edinburgh.

Wood.—On March 21, 1960, at 2, Cross Park, Teignmouth, Devon, Joseph Arthur Wood, M.B., B.Ch., late of Rollrights, Milford-on-Sea, Hants, and Mayfield, Ludlow, Salop, aged 85.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Blood Transfusion in Head Injury

Q.—*Should a blood transfusion be given in cases of head injury ?*

A.—The object of blood transfusion in injured patients is to restore the red-cell and plasma volumes to normal and so to reverse or prevent the haemodynamic effects of acute oligaemia and acute anaemia. Sufficient haemorrhage must therefore have occurred or be occurring to warrant transfusion. There are two main haemodynamic effects of acute oligaemia: an acute reduction in cardiac output and a redistribution of the latter through regional vasoconstriction. Vasoconstriction affects mainly the kidneys and liver-splanchnic flow but not the brain. Reduction of renal and splanchnic blood supply (normally together about one-half of the normal cardiac output) to perhaps 10% or 20% of normal permits the brain (and myocardium) to continue to have a more or less normal blood supply for a time. This unstable state is upset when there is a significant fall in blood pressure. When that occurs the blood supply to these vital organs becomes reduced, and cerebral and cardiac effects, including clouding of consciousness or unconsciousness, occur. Death may then be threatened or imminent.

How is this relevant to patients with known or suspected head injuries ? There are three main groups of cases.

1. Patients rendered unconscious with an obvious head injury who have no injuries elsewhere. Transfusion is not indicated unless the blood loss from the fractured skull (bleeding from the mouth, ear, etc.) is significant or serious. Much of the blood may of course have been swallowed.

2. Patients with a head injury and important injuries elsewhere. The blood loss from the combined injuries must be restored by transfusion. Hesitancy in doing this, on the grounds that further intracranial haemorrhage may occur, is unwarranted, because, as noted above, the brain continues to receive its normal blood supply until the blood pressure falls and death is threatened or imminent from cerebral or myocardial ischaemia.

3. Patients admitted unconscious after an accident when head injury is possible but not definite and there is no obvious cause for the unconsciousness. The differential diagnosis of post-traumatic unconsciousness includes cerebral ischaemia after the haemodynamic effects of a hidden haemorrhage (e.g., intraperitoneal). In such cases a careful therapeutic trial of blood transfusion is indicated, noting the clinical and cerebral responses to, say, one or two bottles of blood. If consciousness returns, head injury is eliminated and the location of the haemorrhage may be determined (e.g., a ruptured spleen); surgical intervention may then be possible. If there is no clinical improvement other causes of coma, including cerebral injury, must be sought for by other means. In these circumstances care must be taken, of course, not to overload the patient with blood. The questioner is recommended to read *Modern Trends in Accident Surgery and Medicine*.[1]

REFERENCE

[1] *Modern Trends in Accident Surgery and Medicine*, 1959, edited by R. Clarke, F. G. Badger, and S. Sevitt, chap. 2-5. Butterworth, London.

Conjugated Oestrogens and Coagulation

Q.—*What is the mode of action of conjugated oestrogens on the coagulation of blood ?*

A.—There does not appear to be any good evidence of a definite effect of conjugated oestrogens on the clotting of human blood with or without a coagulation defect. A number of observers have claimed that conjugated oestrogens (especially intravenously) do aid in haemostasis (particularly in epistaxis and post-tonsillectomy and adenoidectomy bleeding) and that they may shorten an abnormally long bleeding time. Benefit has also been claimed in the treatment of hereditary haemorrhagic telangiectasia. None of these claims appears to be very well established, because the trials of the material have not been controlled. But some effect might be demonstrated were such trials carried out carefully.

Oestrogens, especially intravenously, have also been claimed,[1] with rather better evidence, to be helpful in reducing the blood loss associated with certain gynaecological conditions.

REFERENCE

[1] Greenblatt, R. B., and Barfield, W. E., *J. clin. Endocr.*, 1951, **11**, 821.

Eosinophil Levels

Q.—*What physiological or pathological factors influence the number of eosinophils in the blood, and how do they operate ?*

A.—The answer to this question is still not established with certainty, despite a very large number of contributory investigations. In a symposium on eosinophils published in 1957[1] several hundred observations relating to variations in eosinophil levels were discussed. It is clear that peripheral eosinophilia or eosinopenia may be produced by very many disease processes and experimental procedures. Do these multiple states influence the eosinophil level by diverse means, or do they operate through a common pathway, perhaps by altering the concentration of physiological substances regulating eosinophil numbers ? The latter seems the more likely suggestion, and there are grounds for believing that histamine may be perhaps the most important of the physiological factors concerned.[2–4]

The common occurrence of eosinophils in allergic states and in parasitic infestations suggests that the eosinophils may play a part in the response to foreign protein reactions, in which histamine is known to be concerned, and there is evidence that they appear at sites of local histamine concentration and may exert an antihistamine effect. It is possible that the level of blood histamine may provide a control over the release of eosinophils from the bone marrow, more cells emerging into the peripheral blood when the histamine concentration rises and fewer when it falls. Since the glucocorticoids are known to inhibit the biogenesis of histamine, the eosinopenia occurring in states of stress and induced by glucocorticoids may then be due to a fall in the level of histamine in the blood.

This hypothesis has the merit of integrating a mass of accumulated data on the varying eosinophil reaction to numerous stimuli, those inducing eosinophilia being generally such as to involve histamine release in the course of immuno-allergic responses and those inducing eosinopenia having an action explicable on the basis of glucocorticoid release and consequent decrease in blood histamine. Nevertheless, there are experimental results apparently in conflict with this hypothesis and it cannot yet be accepted as proved.

REFERENCES

[1] *Sang*, 1957, **28**, 389.
[2] Archer, R. K., *J. Path. Bact.*, 1956, **72**, 87.
[3] —— ibid., 1957, **74**, 387.
[4] —— ibid., 1959, **78**, 95.

Tearing of the Hymen

Q.—*Could the use of an internal sanitary tampon rupture the hymen ? If so, could a tear due to intercourse in the hymen of a girl aged 14 or 15 be differentiated from one due to the repeated use of tampons ? How else may the hymen be torn ?*

A.—The hymen varies in size, shape, and consistency. Exceptionally it is so elastic that it remains intact despite repeated coitus and even despite childbirth. Usually coitus tears the hymen and childbirth destroys it, except for the persistence of tags (carunculae myrtiformes). The

insertion of internal tampons can tear the hymen; so can the introduction of one or more fingers, whether inserted for medical purposes or otherwise. As to whether a torn hymen has been caused by tampons or by repeated coitus, in the latter case the introitus and the vaginal canal will probably show a greater degree of dilatation and the tear or tears will be more likely to extend to the base of the hymeneal ring. Reddening of the edges of the tear suggests trauma of recent origin, in which case, in girls of the ages quoted, there might also be local bruising or abrasion to be seen after first coitus. It is very doubtful whether athletic pursuits ever cause rupture of the hymen.

Noise Apparatus for Stammering

Q.—*A stammering boy, aged 15, listens to a noise apparatus, which is variable in pitch and intensity, through stethoscope ear-phones. After using the apparatus for about 15 minutes he complains of tinnitus, lasting for about 12 hours. The apparatus is a great help in the treatment of his condition. What might be the dangers to his hearing from it, and how could they best be avoided?*

A.—The danger to this boy's hearing from any form of noise apparatus depends partly upon the intensity of noise used and very largely upon his individual susceptibility to noise. The main effect of such noise is likely to be that upon his hearing, and in cases of "acoustic trauma" the earliest detectable effect is usually a loss of high tones at a level of about 4,000 cycles per second. He should be tested on a pure tone audiometer immediately before exposure to noise and retested a few minutes after the treatment is finished. If this shows any loss of hearing in the high tones, the intensity level of the noise apparatus should be reduced to one which is found audiometrically to produce no hearing loss.

The tinnitus itself, provided that it recovers and is not accompanied by deafness, should not preclude the use of the apparatus if it is found to be of value in the treatment for his stammering.

Precipitate in Linctus

Q.—*A tarry liquid separates out on standing from a linctus consisting of tinct. chlor. et morph. co. 10 min., syrup. tolu. 30 min., water to 1 dr. What is it? Should it be discarded or shaken up into the mixture?*

A.—The dark, tarry liquid is probably a mixture of resin and chlorophyll precipitated from the tincture of cannabis present in the compound tincture of chloroform and morphine. If mucilage of acacia is added (1 fluid drachm per fluid ounce of mixture) this precipitation does not occur and a uniform mixture results. The mucilage should be mixed with the syrup and the tincture added last.

Cholinergic Urticaria

Q.—*A 15-year-old boy comes out in massive urticaria after strenuous exercise. The eyes are closed by the oedematous lids. The condition passes off in 24 hours, and antihistamines before exercise minimize the reaction. What is the aetiology and treatment of this condition?*

A.—This type of urticaria, usually seen in adolescents, is termed cholinergic urticaria. It is an exaggerated physiological response to heat or exercise or emotional stimuli, and the mechanism involves the release of acetylcholine, though the ultimate wealing is dependent, as always, upon the presence of histamine. It has been shown that in many cases there is a lowered serum cholinesterase, and the administration of anticholinergic agents such as atropine or probanthine may prevent the response for a limited period.[1,2]

There is only very slight, if any, response to antihistamines in ordinary dosage, and the treatment of such patients is difficult. The tendency to the reaction often persists for years. The administration of propantheline, 15 mg. three times a day after meals, and promethazine, 25 to 50 mg. at night, may be of some assistance. Garretts[3] recently reported good results from exfoliation of the skin by ultraviolet light therapy on the basis of the reaction being allied to that of prickly heat.

REFERENCES

1 Grant, R. T., Pearson, R. S. B., and Comeau, W. J., *Clin. Sci.*, 1936, **2**, 253.
2 Morgan, J. K., *J. invest. Derm.*, 1953, **21**, 173.
3 Garretts, M., *Brit. J. Derm.*, 1958, **70**, 166.

Xanthelasma

Q.—*Are xanthelasmas of the eyelids capable of spontaneous resorption? Is there any chemical similarity between the deposits in xanthelasma and atheroma?*

A.—Xanthelasmas of the eyelids are lipoid deposits similar in character to those found in the vessels in atherosclerosis. They are occasionally due to hypercholesterolaemia (as in diabetes), but commonly to local degenerative changes in the eyelids. Once deposited, spontaneous resorption is very unlikely to occur.

Oxaluria in Children

Q.—*Is oxaluria in children of any significance?*

A.—Oxaluria is of no significance in children in the vast majority of cases. It is, in fact, not mentioned in most textbooks on children's diseases and generally it can safely be ignored. There is, however, a rare condition, which has been found mostly in boys, known as oxalosis. It is probably a congenital familial metabolic defect. It shows itself by haematuria, the passage of renal calculi, and a high excretion of oxalic acid in the urine. It terminates with nephrocalcinosis and renal failure.

Explosiveness of Sodium Azide

Q.—*Are laboratory workers exposed to a risk of explosion when using sodium azide as a reagent either in solid form or in solution?*

A.—Sodium azide is less likely to give rise to explosion than, for example, lead azide, which is among the substances used as detonators for purposes of war. No special precautions are taken by suppliers when sending sodium azide to laboratories, but when handling the compound in solid form in the laboratory care should be taken to avoid conditions which might cause explosion. In solution the hazard is small, but, since sodium azide is a strong reducing agent, it should not be mixed with any strong oxidizing agent.

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